A Snapshot of Federal Research on Food Allergy

IMPLICATIONS FOR GENETICALLY MODIFIED FOOD

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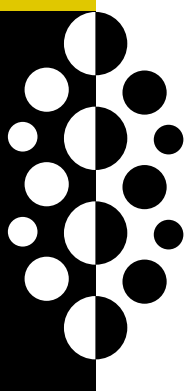

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Contents

Figures and Tables

TABLES

FIGURES

Preface

Although allergies to food have been with us for a long time, we know little about the fundamental mechanism by which people develop allergic reactions to specific proteins in food. Fortunately, many cases of exposure can be prevented because the major food allergens are well known; peanuts and other nuts, as well as cow milk, are common ingredients known to cause allergic reactions in many people. However, despite increased awareness and labeling efforts, food allergy remains a public health problem, accounting for an estimated 29,000 severe allergic food reactions each year, including 150 deaths.

The use of biotechnology in food raises several issues relevant to food allergies. On the one hand, biotechnology may be able to modify foods to remove or change the proteins that cause allergy, offering the potential of making nutritious foods available to people who presently cannot eat them. Research exploring this possibility is ongoing.

On the other hand, biotechnology may also increase the potential risk of food allergy. The ability of biotechnology to move genes from one organism into another creates the possibility of introducing allergenic proteins into foods that would not ordinarily contain them. When the source of an introduced gene is a food known to have allergenic potential, product developers can readily test the genetically modified food to see if the allergenic properties have indeed been carried over into the new variety. Under current Food and Drug Administration (FDA) guidelines, a genetically modified food must be labeled if the new variety contains an allergenic substance that a consumer would not ordinarily expect to find in that food.

The more difficult issue is posed by the introduction of novel proteins that have not been previously in the food supply. Without prior exposure data, the ability to predict the potential of the protein to cause an allergic reaction is very limited. This problem became readily apparent in the recent recall of food products that had been inadvertently contaminated with StarLink, a genetically modified corn variety that had not been approved for human food by the Environmental Protection Agency (EPA) because it could not be shown that the novel protein in StarLink was not an allergen.

With new genetically modified foods under development, some of which could involve novel proteins, what is being done to improve scientists' ability to understand and predict the allergenic potential of new proteins? This is a key question for food safety regulators. To find the answer to this question, the Pew Initiative on Food and Biotechnology commissioned Dr. Lynn Goldman, Professor of Public Health at Johns Hopkins University, to conduct a study of ongoing federal research efforts. While the report finds a variety of food allergy research projects scattered over several federal agencies, Dr. Goldman and her co-author Dr. Luca Bucchini conclude that both the level of funding and the type of research being funded are unlikely to substantially advance scientific knowledge on this key question and therefore will not address fully the needs of food safety regulators. Given the millions of dollars invested in the development of new biotechnology food products, and the importance of maintaining consumer confidence in the safety of the food supply, increased research attention to this issue appears warranted.

The findings of this report, combined with the proceedings of a recent scientific meeting on food allergy sponsored by the National Institute of Environmental Health Sciences (NIEHS), suggest that an expanded and coordinated research effort could provide significant dividends in developing a more robust method for understanding and predicting potential new food allergens. We intend for this report, together with the proceedings of the recent NIEHS meeting, to serve as a mechanism for raising these important concerns with policymakers, industry, and federal agencies and to catalyze further debate and discussion on the issue.

Michael Rodemeyer
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ABSTRACT

Food allergy is an important public health concern. Today, our scientific understanding of food allergy is incomplete, making it difficult for food regulatory agencies to evaluate the potential allergenicity of novel foods. This is of particular concern as agricultural biotechnology products become more prevalent in the food supply. Given the important public policy implications of food allergy research and its use in food safety regulation, the authors undertook a study to assess the federal role in supporting and conducting food allergy research. They identified only thirty-three food allergy research projects with active federal support in the third quarter of 2001. The total commitment of resources at that time was estimated to be, at most, $7 million. The research is spread among four federal agencies (National Institutes of Health, U.S. Department of Agriculture, Food and Drug Administration, Centers for Disease Control and Prevention) with little coordination. A number of important areas of scientific investigation are either not being addressed or are receiving very limited federal attention. The authors conclude that current federal efforts are insufficient to provide the timely and comprehensive information needed by food safety regulators. They suggest that a coordinated federal food allergy research agenda be developed that clarifies the near-term scientific goals, the funding level needed to achieve them, and the role of each federal agency in supporting such work.

Given the important public policy implications of food allergy research and its use in food safety regulation, the authors undertook a study to assess the federal role in supporting and conducting food allergy research.

Introduction

FOOD ALLERGY IMPACT ON HEALTH

Food allergy places a significant health, emotional, and economic burden on the people affected and their families. Individuals with food allergy are at risk of anaphylactic (allergic) reactions if they ingest food to which they are sensitive. Reactions range from mild symptoms such as a skin rash to life-threatening anaphylactic shock. Even minute quantities of a food have been known to trigger allergic reactions in sensitized individuals. Children are at highest risk of death from food allergy (Sampson 1992).

At present, there is no cure for food allergy. The only mechanism for managing the disease is to avoid consuming foods that contain the allergen. If an exposure does occur, the individual must be treated promptly with an epinephrine injection to prevent the possibility of anaphylactic shock and death. These methods are imperfect. Inadvertent consumption of known allergens can occur, particularly when dining away from home. In addition, affected individuals may not consistently carry epinephrine with them. Even when they do, prompt administration of the drug is not always lifesaving (Bock 2001).

The best available data indicate that, on average, 150 people die each year in the United States of food-related allergic reactions and 29,000 have a severe anaphylactic episode (Bock 2001). Some estimates suggest that as many as three million people are allergic to peanuts or tree nuts (Sicherer 1999) and the total number suffering from food allergy is unknown. Due to the serious public health concern presented by food allergy, federal regulators require labeling of foods that contain known food allergens. Thus, by closely scrutinizing food labels, susceptible individuals can hope to avoid potentially life-threatening exposures.

The application of biotechnology to agricultural products presents new challenges to this regulatory scheme. Using genetic engineering techniques, researchers can alter the genetic makeup of familiar agricultural plants or animals. These alterations have the potential to significantly impact the allergenicity of food by either removing or adding allergens. In some instances, the goal of biotechnology research is to increase the safety of food products by eliminating food allergens present in foods such as peanuts or milk, thereby helping to reduce inadvertent exposure to these food allergens. Such an outcome would benefit both consumers and manufacturers.

However, regulatory decision makers, public health professionals, product developers, and consumers are concerned that the technology also has the potential to make food less safe if newly added proteins prove to cause allergic reactions once they are introduced to the food supply. For instance, it is possible that known allergens (such as peanut proteins) could be transferred to food previously thought to be safe (such as soybeans) or that entirely novel proteins (not found previously in the food supply) could be introduced (FDA 1992).

The application of biotechnology to agricultural products presents new challenges to this regulatory scheme. Using genetic engineering techniques, researchers can alter the genetic makeup of familiar agricultural plants or animals. These alterations have the potential to significantly impact the allergenicity of food by either removing or adding allergens.

In the first case, that of transferring known allergens to previously safe foods, federal regulators have clear guidelines to assess these foods. Novel foods created through genetic engineering from known food allergens, such as peanuts or milk, must be evaluated to demonstrate that they are not dangerous to susceptible individuals. One often cited example is a case where researchers at a seed company added components of Brazil nuts to soybeans. When they tested the resulting soybeans with blood serum from people allergic to Brazil nuts, the scientists found cross-reactivity, indicating the presence of an allergen in the engineered soybean. Although these corporate researchers could have gone forward with their work – the resulting product would have simply fallen under the appropriate food labeling provisions – they chose instead to abandon further development of the product to ensure that it did not enter the food supply.

The second example, in which a novel antigen was introduced, is much more difficult for both researchers and regulators to evaluate. Presently, there is no definitive test to determine the potential allergenicity of a novel protein. (EPA, 2000a) Instead, regulatory agencies weigh a number of risk factors which, taken together, provide a rough guide as to the likelihood of allergenicity. These factors include comparisons to characteristics of known allergenic proteins, such as whether a protein resists digestion, is similar in molecular weight or composition, or whether it produces an immunological response in laboratory rats. (EPA, 2000a) The Environmental Protection Agency (EPA) reviews the potential allergenicity of novel proteins that act as pesticides in genetically modified food crops, while the Food and Drug Administration (FDA) reviews allergenicity data for genetically modified food crops containing non-pesticidal proteins under a voluntary industry consultation process.

Aventis CropScience applied for EPA's approval of StarLink corn that carried Cry9C, a protein that confers resistance to the European corn borer, a significant corn pest. Cry9C had not been present previously in the food supply and its allergenic potential was unknown. Cry9C does have some characteristics of an allergen, such as resistance to digestion, that raised concerns about its allergenicity. However, no definitive tests proved either that it is an allergen or that it is not. In the absence of reliable scientific information, regulators were unable to demonstrate its safety, as is required by law, and were forced to deny its use for human consumption. It was, however, approved for use as animal feed. Unfortunately, somewhere in the supply chain, StarLink corn was mixed in with food products that then made their way onto grocery store shelves. Once again, the technology developers and regulators could neither prove nor disprove that StarLink presented a clear public health threat (EPA 2000). As a result, regulators determined that they could not approve its presence in the food supply and they worked with Aventis, grain handlers, and food manufacturers to contain its spread. Although this event did not result in a public health crisis – no proven adverse reactions to StarLink have been documented – it did have significant economic and public relations repercussions for the industry and for federal regulators.

The StarLink example highlights a wide range of issues concerning the regulation and oversight of agricultural biotechnology products (Taylor 2001). One key lesson is that federal regulatory agencies need better scientific tools and knowledge to fully assess the allergenic potential of novel proteins in food (Bucchini 2002; Taylor 2001). This gap in our understanding of food allergy is particularly critical as genetically modified products that contain novel proteins continue to be developed for the market. It is important to note, however, that understanding food allergy and being able to predict and test for safety is also an issue for new foods developed by conventional breeding methods or those introduced to the U.S. population through expanded world trade in agriculture.

FOOD ALLERGY RESEARCH NEEDS

To properly regulate novel food products and protect public health, scientists, health professionals, and regulators must be able to predict whether new proteins introduced to food have the potential to cause allergic reactions in susceptible individuals. To make such predictions we need to understand what characteristics make a protein allergenic, how people become sensitized to food allergens, how allergic reactions are triggered, and whether safe levels of a potential allergen can be established. Furthermore, we need a comprehensive picture of the prevalence and incidence of food allergy in the U.S. population and how it is changing over time. This last point may be of particular importance as we continue to add novel foods to our diet.

Although scientists and health professionals have been working on answers to these questions for some time, our understanding of food allergy is still far from complete. For instance, we do not yet know why some people develop food allergy and others do not. We have known for some time that most people with food allergy have a family history of other allergic diseases such as atopic dermatitis (eczema), allergic rhinitis, and asthma, indicating a genetic role for the development of allergies, including food allergy. Indeed, recent studies have identified a clear genetic predisposition to peanut allergy (Sicherer 2000). However, investigations of the genetics of asthma have proven to be complex and hint that the genetics underlying food allergy may be as well (Barnes 2000.) In particular, we know that genetics is only one element in creating a susceptible individual; early life exposure to the antigen may also be an important factor in the development of subsequent food allergy (Vadas 2001).

We also do not yet fully understand what causes some food proteins to be allergens while the vast majority of food proteins do not trigger allergic reactions. We do know that the immune system in the digestive tract of sensitive individuals recognizes certain proteins as foreign and mounts an allergic immune response. Particular characteristics of these proteins may be responsible for their

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allergenic potential, however, what those characteristics may be is not entirely clear. One avenue of investigation is to fully characterize known food allergens and look for common features among them. Such knowledge could help predict the allergenic potential of new proteins and would help food regulatory agencies assess the safety of novel products.

Researchers and policy makers also lack robust and reliable data on the prevalence (total cases), incidence (new cases per year), and trends of food allergy. As a result, it has been difficult to evaluate the health and economic burden of food allergy or to determine if food allergy is growing as a public health concern. Tracking data on other allergic diseases indicate that the incidence of these diseases is on the rise and experts are concerned that a similar trend may be occurring with food allergy (Beasely 2000; Peterson 1996). However, without the appropriate comprehensive epidemiological data, no conclusions can be drawn.

Finally, it is important to note that private researchers have made some noteworthy contributions to the existing body of knowledge about food allergy. Allergenicity research conducted as part of the brazil nut and Starlink scenarios mentioned earlier in this report, for instance, was carried out in corporate laboratories. This report, however, does not attempt to capture research conducted by the private sector. Although many companies choose to share their data by publishing in peer-reviewed journals, much of the privately-funded research is not made public, nor is it readily available through a tracking mechanism. In addition, this report focuses on the basic research needed to understand the scientific underpinnings of food allergies and to assist regulators in assessing food allergy risks, historically a role for government funded research. Much of the private sector research is aimed at product development and may not be widely applicable. Consequently, we believe that an analysis of publicly funded research serves as an important measure of the public commitment to gathering information about food allergy for policymakers and regulators.

In summary, there are many gaps in the understanding of food allergy, including the causes, mechanisms, and trends of the disease. This deficit has left food safety regulators without some of the critical tools they need to fully assess the potential allergenicity of novel food products, particularly those developed through biotechnology. Recent advances in deciphering the genetic component of disease, the functioning of the immune system, and the mechanisms underlying other allergic diseases provide a rich foundation for making significant strides in our understanding of food allergy. Given the current state of knowledge, the opportunities for progress, and the particular needs of food safety regulators, it is appropriate to ask both what the current federal role is in supporting food allergy research, and – given the current commitment of resources – if we can expect to have the necessary information that would allow for sound regulatory decision making.

In summary, there are many gaps in the understanding of food allergy, including the causes, mechanisms, and trends of the disease. This deficit has left food safety regulators without some of the critical tools they need to fully assess the potential allergenicity of novel food products, particularly those developed through biotechnology.

The analysis described in this paper takes a snapshot of federal food allergy research and explores these questions. The study is limited in both time and scope, and therefore does not provide cumulative information or data on research performed with resources other than federal funding. It is also important to understand that this review used a very strict definition of food allergy related research. Basic research into allergic response – such as ongoing NIH studies into genetics and other interactions that determine what proteins induce an Immunoglobulin E (IgE) antibody response – were not included. Nor did the analysis include studies of other allergic diseases. It should be noted that these other NIH studies may provide critical information that, in the future, could improve the understanding of allergenicity in food. Nonetheless, this study is an important first step in promoting a discussion of the federal commitment to food allergy research.

Data Sources

For the purpose of this study, food allergy research is defined as research funded by the federal government and aimed at investigating food allergy, where food allergy is an immune-mediated disease caused by food antigens. This is similar to how the National Institute of Allergy and Infectious Diseases (NIAID) classifies food allergy research. We relied on data in two publicly available databases: CRISP (Computer Retrieval of Information on Scientific Projects, http://crisp.cit.nih.gov), a database of research supported by the Department of Health and Human Services (HHS), and CRIS (Current Research Information System, http://cris.csrees.usda.gov), a database of projects supported by the United States Department of Agriculture (USDA). In addition, we contacted knowledgeable individuals in each federal agency to ensure that we retrieved a comprehensive list of projects. We obtained information on the expenditures for each project from the agencies. (For details of how research was abstracted, classified, and analyzed, please refer to Appendix I.) Together, these sources allowed us to identify all federally supported food allergy research, both extramural (performed with government grants and contracts) and intramural (performed in government laboratories).

Due to how data is maintained in CRIS and CRISP, this study captures research projects that were active during the third quarter of 2001. It does not account for studies that may have just been completed or that will soon be approved. The analysis also does not provide information on when these studies may have begun, when they may end, or when funding was first committed for them. Therefore, this data cannot be used to estimate quarterly or annual federal commitments of funds for food allergy research. As a snapshot, it also excludes projects that may be relevant to food allergy in the long run but were not identified as such by the chosen inclusion criteria.

TABLE 1 Summary of Federal Food Allergy Research (intramural and extramural)

Agency	Total No. of Studies	Institutes/ Programs	Areas of Interest for Food Allergy	Number of Studies	Funding
CDC** *Centers for Disease Control and Prevention*	1		Surveillance and epidemiology	1	0+
EPA *Environmental Protection Agency*	0		Risk assessment and regulatory approvals	0	0
FDA** *Food and Drug Administration*	4		Food safety, risk Assessment, labeling	4	$295,500
NIH** *National Institutes of Health*	22	Allergy and Infectious Diseases	Allergy science, treatment, and prevention	11	$2,257,779
		Diabetes and Digestive and Kidney Diseases	GI disease science, treatment, and prevention	1	N/A*
		Heart, Lung, and Blood	Food allergy in relation to asthma	2	$1,014,625
		National Center for Research Resources	Support of clinical investigative research	8	N/A*
		Environmental Health Sciences	Environmental science and risk assessment	0	0
		Child Health and Human Development	Child health science, treatment, and prevention	0	0
USDA *U.S. Department of Agriculture*	6	Cooperative State Research, Education, and Extension Service	Nutrition, food safety, and health	3	$587,116
		Agricultural Research Service	Food consumption, nutrition, and food safety	2	N/A*
		Other Cooperating Institutions		1	N/A*
N	**33**				
Total $					**$4,155,020**

* Not available.

\+ CDC staff are working on an objective for Healthy People 2010 - the characterization of food allergy deaths; however, the agency does not have funding to pursue this work. (See Appendix II for details.)

** CDC, FDA and NIH are separate agencies under the Department of Health & Human Services

Finally, this analysis does not describe research supported by industry, private non-profit organizations, or states. Nor does it consider international research that may contribute to our understanding of food allergy. All of these sources may have a significant impact on the advancement of food allergy research that regulatory agencies could draw upon.

Findings

FEDERAL SUPPORT IS LIMITED

Only thirty-three food allergy research projects were identified through CRISP, CRIS, and interaction with the agencies. Table 1 shows the total number of studies by agency. (Appendix II provides a complete listing of the studies identified and other detailed results.)

Only $4.2 million in expenditures for food allergy research were identified. However, this amount represents only a portion of the total federal expenditure because budget details were not available for a number of studies. Estimates from the available budget information suggest that no more than a total of $7 million in federal support was provided to the food allergy research projects identified in this analysis.[1]

RESEARCH IS SPREAD THIN WITH LITTLE COORDINATION

As shown in Table 1, a combination of nine different agencies and institutes supervise the few studies on food allergy conducted with federal support. Within these organizations, some of the research is conducted in government laboratories and some is performed under grants or contracts to universities. Each agency has a different interest in the issue and on one level, it is very important that these interests are pursued. However, given the small overall investment in this area, it is clear that research resources are spread very thin. This is true even within the National Institutes of Health (NIH) which supports twenty-two of the thirty-three studies identified but has spread them among four different institutes (Table 1).

1. Since the time of our analysis, one additional project was funded by USDA, a study directed to the development of an animal model for food allergy, which was funded at $784,000 for thirty-six months.

Each agency has a different interest in the issue and on one level, it is very important that these interests are pursued. However, given the small overall investment in this area, it is clear that research resources are spread very thin.

There are four important categories of research for all allergic diseases: **causes (etiology), prevention, pathophysiology/treatment,** and **surveillance (epidemiology).** The emphasis of the work identified in this study is on causes and pathophysiology/treatment. Very few focus on prevention or surveillance. Where epidemiological information is collected, we found that it is either inadequate to fully inform our understanding of food allergy or has never been analyzed or used by federal agencies. (See the discussion in Appendix II of the food allergy studies in Healthy People 2010 and NHANES at CDC and CSFII at USDA.)

Even where experts in the field have identified research needs and opportunities, as was done in 1997 under the auspices of NIAID (Plaut 1997), the federal portfolio falls short of addressing all of the important research topics. (See Appendix II.) While a number of priority topics do receive support, there are nearly as many studies on topics that do not appear on this 1997 list. This indicates either that research advances have eclipsed the priorities identified in 1997 and, therefore, it is time to revisit the question, or that current mechanisms used to make funding decisions, while generally effective for identifying the highest quality of research, have not resulted in a research portfolio that focuses on this priority research topic. (This is not to say that the NIH mechanisms for funding peer reviewed research are inappropriate but rather to point to a need to encourage increased activity in this area by the academic community.)

TABLE 2 Federal Food Allergy Research Focuses on Common Allergens

Type of allergenic food	CDC + FDA	NIH	USDA	Total
Corn	1	1		2
Infant Formula		1		1
Milk		6		6
*Nuts**		1	1	2
Peanut	1	6	4	11
Several Foods	3	2	1	6
Not Determined		5		5
TOTAL				**33**

* *Nuts includes walnuts and other tree nuts.*

Important categories of research — such as epidemiology — are not properly addressed by federal sources and coordination is insufficient to ensure that research needs and opportunities are fully met.

In summary, a small number of studies are spread thinly among a number of agencies and institutes, with many of those performed at universities. Important categories of research – such as epidemiology – are not properly addressed by federal sources and coordination is insufficient to ensure that research needs and opportunities are fully met.

RESEARCH WILL NOT ADDRESS NEEDS FOR BIOTECHNOLOGY REGULATION

Not surprisingly, given its clinical severity, most of the research effort is concentrated on peanut allergy (eleven studies out of thirty-three), particularly from the USDA. Milk, an important cause of pediatric allergies, ranks second (six studies), and corn third (two studies) **(Table 2).** Thus, the majority of studies underway focus on foods that have traditionally caused food allergy (nuts and milk), while there is almost no work exploring the allergenicity of novel proteins in food.

Risk assessment protocols for food allergy examine four elements that contribute to food allergy hazards: **allergenicity assessment** (is the food or elements of the food a potential allergen); **dose response assessment** (is there a safe concentration of an allergen); **exposure assessment** (how likely is it that people will encounter the allergen); and **susceptible subpopulations** (how do those prone to allergy react to this novel food) (NRC 1983; Bucchini 2002). To make sound risk assessments, regulators need to understand each element.

In our analysis, we found that the federal research portfolio on food allergy is incomplete because all four of these elements are not adequately addressed. No studies examine the dose response or exposure assessment information needed for setting "safe" levels for new proteins produced by biotechnology. Efforts to develop animal models or in vitro tests for food allergy are extremely limited in this sample. Furthermore, the studies on identifying and characterizing susceptible subpopulations are insufficient, particularly as epidemiological studies are not well represented in this sample. Finally, there is little research on identification and characterization of new allergens or the molecular determinants of food allergy.

Despite these shortcomings, there are twenty-three studies relevant to biotechnology regulation. Seventeen of these research projects have the potential to yield results usable for allergenicity assessment, five may yield information on susceptible subpopulations, and one may be useful for evaluating the consequences of potential new allergens. It is interesting to note that although FDA and USDA fund relatively few projects – only ten altogether – all ten of these studies are likely to provide information relevant to the regulation of biotechnology. (Appendix II, figure 3 includes additional details.)

In total, current efforts in federal food allergy research appear to be insufficient to produce results that could be applied to allergenic risk assessment in a short interval of time. Therefore, food safety regulators are unlikely to have all of the necessary tools for assessing the potential allergenicity of novel foods such as those created using biotechnology. As a result, some product developers may lack a clear, predictable pathway to the market, and products approved using the information available today may be vulnerable to court challenges in the future *(Harlan Land Co. vs. United States Department of Agriculture, 2001)*.

Conclusions and Recommendations

While several federal agencies contribute independently to food allergy research, it does not appear to be a priority for any of them. There were only thirty-three research projects supported by the federal government at the time this analysis was conducted, with a total research effort in the range of $4.2 to $7 million. This is a limited commitment in relation to both the research needs on this topic and to the total federal commitment to biomedical and related life science research in fiscal year 2001 of $18.2 billion (AAAS 2001).

The NIH leads the way in food allergy research, with most of its effort supported by the National Institute of Allergy and Infectious Diseases (NIAID)[2]. The National Center for Research Resources (NCRR) at NIH also supports a significant portion of the federal food allergy research portfolio. The FDA has a small but focused effort that aims to meet its regulatory needs. The USDA has concentrated on identification of allergens and detection methods, and the analysis of the plants that are the primary source of food allergens. The contributions by other agencies are very small. Thus, the research is spread out among many federal agencies, with little or no coordination among them. On the whole, agencies have not developed specific research goals or objectives for food allergy. Where priorities have been articulated, as at NIAID, the work funded does not fully address the priorities identified.

While some of the projects recognized in this analysis are relevant to the regulatory assessment of new biotechnology products, the sum total of the effort is not adequate to improve sound, science-based regulatory decisions on potential allergenicity. The multifaceted nature of food allergy is probably best addressed by a combination of efforts both on basic research questions and targeted activities to develop needed regulatory assessment tools. The findings of this study demonstrate the value of research funded by the USDA and the FDA to address regulatory needs while

2. Although investment in research specific to food allergy is modest, the total NIH support of research that may become relevant to food allergy is considerably greater given the broader relevance of other research efforts at NIH on how proteins induce immune responses.

NIH supports advances in the understanding of food allergy that forms the basis of safety assessments. However, this report clearly shows that the current funding level at all agencies is insufficient and there is a role for stronger coordination of activities across agencies.

Therefore, we recommend that a process be initiated to develop a coordinated federal food allergy research agenda that clarifies near-term scientific goals, the funding level needed to achieve such goals, and the role of each federal agency in supporting such work. Specifically, we recommend:

1. The development of a comprehensive assessment of current research needs and opportunities, with a particular focus on regulatory needs, with the input of scientists and key agencies.

2. The use of this assessment to develop broad goals and specific near-term research priorities. Goals may include: generating valid scientific information to develop effective and protective regulation of potential new allergens; determining the cause of food allergy and developing interventions to prevent its initial occurrence; reducing the burden of food allergy for people with the disease; preventing anaphylactic episodes and mortality from anaphylaxis; assessing the burden of food allergy in subpopulations; and tracking the disease and assessing the effectiveness of food allergy programs.

3. The development of shared goals and strategies among federal agencies that assign specific objectives to each agency. Designate a lead agency and encourage the involvement of private and non-profit parties wherever possible. Cooperation could achieve an optimum whereby research would be useful both for the scientific and public health communities.

4. A determination be made of the funding levels needed to achieve the stated research priorities in a specified period of time and a commitment made of the appropriate level of funds each year until the goals are achieved.

When agricultural biotechnology moved from the laboratory into the field and then to the marketplace, policymakers and the public challenged food allergy scientists to answer new questions and apply what they knew to novel situations. All of the participants in this debate, whether scientists, policy makers, the public, or biotechnology developers, have a stake in the development of the necessary information to ensure that regulators are making sound, predictable regulatory decisions. Current advances in biomedical and public health research offer a tremendous opportunity to meet the scientific challenges raised by biotechnology in relation to food allergy. A coordinated and focused effort by federal agencies to support the science needed to resolve these questions would pay large dividends to all stakeholders – including helping to avoid the kinds of economic losses and negative impact on public trust seen with StarLink corn.

All of the participants in this debate, whether scientists, policy makers, the public, or biotechnology developers, have a stake in the development of the necessary information to ensure that regulators are making sound, predictable regulatory decisions.

Appendix I - Methods

DEFINITIONS

For the purpose of this study we defined food allergy research as research funded by the federal government that focuses on food allergy, where food allergy is an Immunoglobulin E (IgE) mediated disease caused by food antigens. There is also federally supported research directed at the understanding of allergic diseases in general. Although such studies may improve the understanding of the mechanisms underlying food allergy, such studies are less likely to lead directly to the elucidation of the specific causes of food allergy or to better methods of prevention. Therefore, we excluded such studies from this analysis. The definition of food allergy research adopted here is similar to that used by the National Institute of Allergy and Infectious Diseases (NIAID). Specifically, within NIAID there are studies on mechanisms and clinical trials for other allergic diseases that are potentially relevant to food allergy, but these studies are not included in the NIAID tallies of the food allergy research it supports.

DATA SOURCES

We used two publicly available databases to identify food allergy research supported by federal sources. CRISP (Computer Retrieval of Information on Scientific Projects, http://crisp.cit.nih.gov/) contains information on research projects and programs supported by the Department of Health and Human Services (HHS). It includes information on intramural programs of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) and on extramural projects, grants, contracts, and cooperative agreements funded by the NIH and other government agencies (Centers for Disease Control and Prevention, FDA, Health Resources and Services Administration, Agency for Health Care Policy and Research). The projects were primarily conducted by universities, hospitals, and other research institutions (Finch 2001a). The database is updated weekly (Finch 2001b). In this study, a CRISP database query was run in the third quarter of 2001 and all studies listed as current projects at that time were considered for analysis.

CRIS (Current Research Information System, http://cris.csrees.usda.gov/) is “the U.S. Department of Agriculture’s (USDA) documentation and reporting system for ongoing and recently completed research projects in agriculture, food and nutrition, and forestry” (emphasis added). The database includes projects directly conducted or sponsored by USDA research agencies, state agricultural experiment stations, the state land-grant university system, other cooperating state institutions, and participants in a number of USDA research grant programs. CRIS is a part of Science and Education Resources Development (SERD), Cooperative State Research, Education, and Extension

Service (CSREES). In this study, a CRIS database query was run in the third quarter of 2001 and all studies listed at that time were considered in this analysis. CRIS and CRISP staff ensured the validity of the research methods.

Other documents used in this research included *NIAID: Planning for the 21st Century* (NIAID 2000), *The Federal Asthma Research Agenda* (Locke 2000), and other scientific papers as cited. We based the relevance of each research study to food allergy on the abstracts in CRISP and CRIS, which were written by the studies' investigators. However, our review of the abstracts resulted in slight differences between our categorization and that of an independent NIAID search of their projects; our classification process resulted in the inclusion of two additional studies when compared to the NIAID analysis. Where available, details on the expenditures for each project were obtained from the agencies. Combined, these sources allowed us to identify all of the research, both extramural (performed with government grants and contracts) and intramural (performed in government laboratories).

TYPES OF RESEARCH

We analyzed each federally supported food allergy research project to determine the goal of the research (GR), the relevance to research objectives (RO) as set out in Plaut (1997), and the relevance to biotechnology (RB).

The **goal of research (GR)** classification was adapted from the report *Attack on Asthma,* published by the Pew Environmental Health Commission, and was developed by one of the investigators for that report. Studies were categorized according to the questions they address: food allergy etiology (etiological research), food allergy trends in populations (surveillance), food allergy-related preventive and community-based interventions (prevention), food allergy mechanisms of disease (pathophysiology) and treatment mechanisms (treatment). Specifically, the definitions below were used for each category:

Etiological research concerns the causes of food allergy. Projects were more finely categorized as to whether they intend to study environmental, genetic, and other (including gene-environment interactions) determinants of disease. For example, a project that seeks to identify the molecular characteristics of allergens was classified as etiological, with an environmental focus.

Surveillance involves effort to determine the rates of disease prevalence (number of cases) and incidence (number of new cases in a time period) as well as to characterize the occurrence of disease within population groups, geographic areas, and over time. Examples of surveillance include monitoring of causes of death on death certificates, national surveys like the National

Health Interview Survey, which tracks rates and severity of diseases, and registries like the cancer and birth defects registries that exist in many communities.

Prevention research includes strategies and methods that reduce risk factors, including the organization and evaluation of interactions of medical or public health personnel with the public. The aim is to reduce the burden of food allergy via new intervention methods including education and the creation of networks and partnerships that facilitate care. This definition encompasses research of primary, but also secondary or tertiary prevention.[3] An example of tertiary prevention research is a study aimed at assessing the effectiveness of education to prevent anaphylaxis episodes in allergic patients.

Pathophysiology addresses the body's response to food allergens, including those at a cellular and molecular level, while treatment includes individual, patient-based interventions, including the use of drugs and other therapies. Pathophysiology and treatment were grouped together because advances in understanding of pathophysiology often lead to improved therapy; on the chart they are labeled "treatment".

These definitions are not mutually exclusive and we made an effort to assign each study to the category that appears to be the main purpose of the study. Each assignment is explained in a concise statement that is available for review upon request to the authors.

The **relevance of research objective (RO)** analysis was based on categories described in a paper by Plaut (1997). A group of leading scientists developed these categories when they came together to identify research priorities in the field of food allergy. In his paper, Plaut describes three main areas of emphasis (renamed here):

Molecular determinants of food allergenicity. Projects in this category are designed to address the characteristics that make some foods, or components of foods, allergenic. Such studies include the identification and cloning of allergens; their structural, functional, biochemical, and sequence analysis with systematic comparisons to identify shared features; the identification and characterization of immune responses to IgE binding epitopes; and the manipulation of allergens in genetically modified organisms for the study of food allergy.

Gastrointestinal tract immune responses and food allergy. These studies aim to elucidate the differences in the gastrointestinal immune response between normal individuals and food aller-

3. Primary prevention is that done to prevent the onset of disease before it occurs; secondary aims to identify disease at the earliest stages and arrest its progress before there is damage or death; tertiary prevention is treatment done to minimize the extent of damage or death.

gy patients. (This is somewhat narrower than the category developed by Plaut.) Examples include: the role of bacterial antigens of intestinal flora in food allergy; the mechanism by which food allergy patients do not display oral tolerance; the effects of cytokine manipulation on tolerance; and how the persistence of food allergy differs between allergens (e.g., peanut allergy often lasts a lifetime while milk and egg allergy may not persist past childhood).

New advances in food allergy. These studies explore exciting new "leads" or opportunities in the field. Following Plaut's description, we included studies that address the role of the Histamine-Releasing Factor (HRF) in food allergy, the role of negative signaling and DNA immunization in therapy, the role of humanized anti-IgE antibodies, and genetic studies that address atopic disease and food allergy (this differs from the studies proposed in Plaut).

Others. Includes research projects that do not fit any previous category.

Finally, **relevance to agricultural biotechnology (RB)** was based on a set of criteria developed by the investigators. This categorization scheme was developed from the paradigm of risk-science-based regulation initially formulated by the National Research Council (NRC 1983) and subsequently adopted by regulatory agencies (Bucchini 2002; EPA 2000b; EPA 2001). The elements in this framework are:

Allergenicity assessment (AA) or hazard identification;

Dose response (DR) assessment (for both sensitization and allergic responses);

Exposure assessment (EA);

Susceptible subpopulations (SS); and

Evaluation (or monitoring) is carried out after a decision is made in order to inform the next round of decision making in the risk assessment process.

Each food allergy research project identified in this analysis was assessed to determine if it addressed one of these five elements. If a study addressed any of these elements it was determined to be relevant to the regulation of agricultural biotechnology. By default, if studies could not be assigned to any of these categories, they were excluded from the relevance to biotechnology analysis.

Appendix II – Results

Only thirty-three food allergy research projects were identified. Several federal agencies contribute to their funding. These thirty-three projects fulfilled the inclusion criteria: they fit the definition of food allergy research and were active at the time of the database searches performed in the third quarter of 2001. Sources of information on research projects include the two databases, CRISP and CRIS, and direct interaction with the agencies. Most studies were identified through the CRISP database, whereas the CRIS database yielded only six studies (the search on CRIS excluded other linked data sets that mirror CRISP). Interestingly, projects performed at the Food and Drug Administration (FDA) were all identified through direct interaction with the agency, and none were included in the CRISP database **(Table 3)**. This was not expected (Finch 2001a). In the following sections, the research projects of each agency are described. Subsequently, the research projects are analyzed by different classification criteria.

TABLE 3 Food Allergy Research Projects by Data Source

Data Soource	N
CRIS (USDA)	6
CRISP (NIH)	22
Personal Communication	5
N	**33**

RESEARCH FUNDED BY FEDERAL AGENCY

The survey revealed that, among federal agencies, the National Institutes of Health (NIH) supports the largest number of food allergy research studies (twenty-two out of thirty-three); the United States Department of Agriculture (USDA) contributes less than a quarter of all projects (six out of thirty-three); the FDA has four projects; the Centers for Disease Control and Prevention (CDC) has one in collaboration with the FDA; while the United States Environmental Protection Agency (EPA) has none **(Table 4)**. Within these agencies, some of the research is conducted at government laboratories and some is performed under grants or contracts to universities. Not surprisingly,

TABLE 4 Food Allergy Research by Funding Agency (intramural and extramural)

Agency	Total No. of Studies	Institutes/Programs	Number of Studies	Funding
CDC	1		1	0+
EPA	0		0	0
FDA	4		4	$295,500
NIH	22			
		NIAID	11	$2,257,779
		NIDDK	1	N/A*
		NHLBI	2	$1,014,625
		NCRR	8	N/A*
		NIEHS	0	0
		NICHHD	0	0
USDA	6			
		CSREES	3	$587,116
		ARS	2	N/A*
		OCI	1	N/A*
N	*34*			
Total $				**$4,155,020**

+ Although CDC is conducting work, they do not have money in their budget to do so.

* Not available.

given its clinical severity, most of the effort is concentrated on peanut allergy (eleven out of thirty-three), particularly at the USDA. Milk, an important cause of pediatric allergies, ranks second, and corn third (Table 2). The following describes the activities of the different federal agencies.

National Institutes of Health (NIH):

The National Institutes of Health is the primary supporter of food allergy research in the United States. Several NIH institutes actively fund research relevant to food allergy. The National Institute of Allergy and Infectious Diseases (NIAID) is the principal supporter of food allergy research with twelve active projects; the National Center for Research Resources (NCRR) funds eight projects (deriving from five supported research centers); the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funds one (of the R01 type)[4]; and the National Heart, Lung, and Blood Institute (NHLBI) funds two (one R01, one U10) **(Table 5)**. In practice, NIAID has awarded only four major grants for food allergy research (the NIDDK and NHLBI grants do not have food allergy as the primary focus).

National Institute of Allergy and Infectious Diseases (NIAID): According to its strategic plan, "NIAID conducts and supports research that strives to understand, treat, and ultimately prevent the myriad infectious, immunologic, and allergic diseases that threaten millions of human lives." In fiscal year 2001, NIAID had a total budget of over $2.069 billion making it the third largest institute at NIH. In the third quarter of 2001, NIAID was supporting one Research Program Projects grant (P01) (accounting for four individual projects), three Research Project Grants (R01), and a total of four K-Series, clinical research career awards (one K08, two K23 and one K24). This amounts to a total of $2,257,779, where information on funding was available.. NIAID is not undertaking any food allergy related intramural research project (which covers 11 percent of its overall budget, [NIAID 2000]), and food allergy is not addressed in any NIAID funded epidemiological studies.

NIAID, with the National Institute of Child Health and Human Development (NICHHD) and NIDDK, invited applications for research studies through its issuance of a Program Announcement, Immunologic Basis of Food Allergy (PA-97-091). Studies that can be considered for funding through this mechanism address the mechanisms of mucosal immunity and of tolerance as they apply to food allergy; the genetic basis of food allergy; the molecular identification of food allergens and their epitopes; and/or immunotherapeutic approaches to treating food allergy. Currently, there are three NIAID individual research (R01) grants (Table 5, ID=10, 15, 16). There is one major program grant (P01), which was awarded to the Mount Sinai School of Medicine in New York and includes four projects relevant to food allergy (ID=8,11,17, 25). There are several career development (K-Series) grants (ID=5, 6, 24, 26). Among the programmatic areas highlighted in PA-97-091, the identification of food allergens and their epitopes are not being pursued in the current NIAID portfolio, although three studies are developing some information related to epitopes. Other areas of potentially important food allergy research are not

4. NIH uses a particular alphanumeric code to identify their many research projects. (See Key Code on page 25 for detailed information)

TABLE 5 Food Allergy Research Projects That Meet the Inclusion Criteria

Agency	Center	ID	Principal Investigator	Project Title	Source	Type
NIH	NIAID	5	Burks, AW	Immunotherapy for patients with peanut anaphylaxis	CRISP	K24
		6	Horner, A	Allergen gene vaccination in mouse model of food allergy	CRISP	K08
		8	Li, X M	Animal model of cow hypersensitivity	CRISP	P01
		10	Liu, FT	Immunological basis of anti IgE immunotherapy*	CRISP	R01
		11	Mayer, L	Oral tolerance and cow milk allergy	CRISP	P01
		15	Rothenberg, M	Regulation of gastrointestinal eosinophils	CRISP	R01
		16	Sampson, H	Immunomodulation of food allergy by DNA based immunity	CRISP	R01
		17	Sampson, H	Cow milk allergens in IgE and non-IgE mediated cow milk allergy	CRISP	P01
		24	Sicherer, S	Genetic basis of peanut allergy	CRISP	K23
		25	Sperber, K	Antigen processing in cow milk allergy	CRISP	P01
		26	Teuber, S	Immunobiology of walnut food allergy	CRISP	K23
	NHLBI	27	Weiss, S	Diet, immune modulation, and asthma in early life	CRISP	R01
		29	Zeiger, RS	Childhood asthma prevention study (CAPS) for PACRN	CRISP	U10
	NIDDK	12	Nagler-Anderson, CR	Altered responses to food proteins in enteric infections	CRISP	R01
	NCRR	3	Assa'ad, A	Effect of allergen elimination diets on asthma and bronchial hyperresponsiveness	CRISP	M01
		7	Lehrer, S	Corn induced allergic responses	CRISP	M01
		18	Sampson, H	Mechanisms of food hypersensitivity in atopic dermatitis	CRISP	M01
		19	Sampson, H	Immunologic basis of cow milk induced hypersensitivity	CRISP	M01
		21	Sampson, H	Allergenicity of aminoacid based formula (neocate 1+)	CRISP	M01
		28	Wood, R	Natural history of peanut allergy	CRISP	M01
		33	Sampson, H	Trial of HU-901 in peanut allergy	CRISP	M01
		35	Liu, A.	IgE isoforms in food induced atopic dermatitis in children	CRISP	M01
FDA	FDA	40	Gendel, S	Sequence database for assessing allergenicity	PC	**
		41	Gendel, S	Comparison of the digestion and acid stability of food allergens and non-allergenic proteins	PC	**
		42	Williams, K	Evaluation and development of an immunochemical test method for food allergens	PC	**
		43	Raybourne, R	Detection of human antibodies against the recombinant food protein, Cry9C	PC	
CDC	NCHS	50	Elliott, E	Healthy People 2010: objective 10.4	PC	**
USDA	ARS	44	Chung, S	Peanut allergenicity	CRIS	**
		45	Chung, S	Peanut allergenicity as affected by end products produced during roasting	CRIS	**
	CSREES	46	Dodo, HW	Reducing peanut food allergy risks	CRIS	**
		48	Kathe, SK	Development of immunoassays for detection of almond and walnut proteins in foods	CRIS	**
		49	Taylor, SL	Allergenic foods: their detection, allergens, and effects of processing and genetic engineering	** CRIS	
	OCI	47	Dodo, HW	Screening commercial peanut for allergen-free peanut plants	CRIS	**

CRISP=NIH CRISP Database, CRIS=USDA CRIS Database, PC=Personal Communication

* Actual year of funding is FY 2001, although the study was found in CRISP 8/2001 (Personal communication, M. Plaut).

** Unlike NIH, neither FDA, CDC nor USDA uses an alphanumeric code to differentiate research projects.

P01 grants are "Research Program Projects," or projects that "provide an institution with support of a multidisciplinary, often long-term research program with a particular objective or theme involving the organized efforts of groups of investigators."

R01 grants are "Research Project Grants" that "provide support to an institution (domestic or foreign) on behalf of a principal investigator for a project proposed by the investigator"; they represent the bulk of NIH research on food allergy.

K-Series grants are mentored awards for: clinical scientist development (K08), patient-oriented research career development for young investigators and mid-career investigators (K23), and those performing patient-oriented research (K24); the primary purpose of these smaller grants is the support of the investigator.

U10 grants are called "Cooperative Clinical Research Cooperative Agreements" and usually indicate that a project intends to carry out a clinical trial on human subjects.

M01 grants are traditionally provided for work conducted at general clinical research program centers.

clearly identified as programmatic priorities in PA-97-091. For example, it is not clear whether studies of environmental exposures (including prenatal ones) or of health disparities could be funded through the current NIAID PA mechanism.

National Heart, Lung, and Blood Institute (NHLBI): The NHLBI is concerned with diseases of the heart, blood vessels, lung, and blood, blood resources, and sleep disorders. It funds two projects on food allergy-one R01 (Table 5, ID=27) and a U10 (ID=29)-that are related to asthma, an area of research and prevention in which NHLBI is actively engaged. The total funding for these studies is $1,014,625.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): The NIDDK's Research Funding Program Areas include "Gastrointestinal Mucosa and Immunology" and "Digestive Diseases and Nutrition Epidemiology and Data Systems." This Institute funds one R01 project, primarily concerned with enteric infections (Table 5, ID=12), the results of which may have some interesting implications for food allergy research. The level of support at NIDDK for food allergy research was not available.

National Center for Research Resources (NCRR): The NCRR complements the activity of other NIH institutes by providing resources for scientific investigations by supporting a number of General Clinical Research Centers (GCRCs). Located in units within hospitals of academic medical centers, this national network of centers provides a research infrastructure for clinical investigators who receive their primary support from NIH institutes or other federal agencies (NCR 2001). Five centers have ongoing food allergy projects funded through this mechanism. The Mount Sinai School of Medicine in New York is the most active GCRC in terms of food allergy research with four studies (Table 5, ID=18, 19, 21, 33). Projects funded through the NCRR address various issues, including: the effects of food allergen elimination (ID=3); corn allergy (ID=7); IgE isoforms in atopic dermatitis (ID=35); and others (ID=18,19, 21, 28, 34). Given the relatively small number of grants provided by other agencies, it appears that NCRR is playing a key role in supporting food allergy research. We were not able to identify the total funding for NCRR food allergy research.

National Institute of Environmental Health Sciences (NIEHS) and National Institute of Child Health and Human Development (NICHHD): NIEHS did not have any ongoing projects on food allergy at the time this analysis was conducted (Dori Germolec, NIEHS, personal communication). This is also true for the NICHHD, despite the fact that food allergy is significantly more prevalent in children than adults and children are most at risk of death from anaphylactic shock.

Food and Drug Administration (FDA):

The Food and Drug Administration (FDA), an agency within HHS, is by law in charge of the safety of most foods. This includes both foods that are naturally allergenic and foods that are potentially allergenic, such as those with additives or biotechnology derived foods (with the exception of biotechnology derived foods that contain engineered pesticides, because they fall primarily under the jurisdiction of the EPA). This responsibility belongs specifically to the FDA's Center for Food Safety and Applied Nutrition (CSFAN).

Although we did not identify food allergy research at FDA in the CRISP database, we identified four research projects underway at the FDA through personal communication with Dr. K. Bunning at CSFAN (Table 5). Two of these projects (ID=40, 41) are underway at the National Center for Food Science and Technology (NCFST), a research consortium of CFSAN, industry, and academia. These projects focus on the development of databases of allergen protein sequences, procedures for using these databases to assess potential allergenicity, and assessment of digestion and stability of food allergen proteins. A third FDA-funded study (ID=42) is evaluating the performance of commercial peanut allergen test kits and new commercial detection methods for other food allergens. The fourth study (ID=43) is addressing the issue of whether StarLink corn exposure was sufficient to create an allergenic sensitivity in the general population.5 Reportedly, FDA funding for all of this research is $295,500.

Centers for Disease Control and Prevention (CDC):

National Center for Environmental Health (NCEH): NCEH worked collaboratively with FDA to investigate the alleged food allergy outbreak associated with StarLink corn (Winterton 2001). Beyond that study, no other research is in place at NCEH that concerns food allergy (C. Rubin, CDC, personal communication). Since the StarLink investigation was concluded at the time this project started, it was not included in this analysis.

National Center for Health Statistics (NCHS): NCHS collects and analyzes vital statistics and "information on health status, lifestyle and exposure to unhealthy influences, the onset and diagnosis of illness and disability, and the use of health care" (NCHS 2001a). NCHS's survey, the National Health and Nutrition Examination Survey (NHANES), collects information on allergies in a representative sample of Americans. In NHANES III (1988-94), selected participants also

5. Although FDA was not supporting other research efforts on food allergy when this analysis was conducted, they do support a number of other activities related to food allergy and regulatory decision making (E. Elliott, FDA, personal communication). Recently, the agency published a draft Compliance Policy Guide (CPG) entitled "Statement of Policy for Labeling and Preventing Cross-Contact of Common Food Allergens" (66 FR 22240; May 3, 2001). The FDA now has a web site on food allergens, www.cfsan.fda.gov/~dms/wh-alrgy.html.

received a peanut skin prick test (NCHS 1994). A positive skin prick test is a marker of food allergy. However, despite the collection of this data, analysis of it is not the subject of any specific NCHS project and thus we did not include this effort in our analysis (K. Turczyn, NCHS, personal communication). On the other hand, NCHS, under the supervision of the FDA, is working on a developmental objective of Healthy People 2010, the national multi-agency effort to promote a common health agenda, related to food allergy, "Food Allergy Deaths" (NCHS 2001b). ("Developmental" means that there was no baseline data.) This objective is based on vital statistics (death certificates) and relies on the recent adoption of the International Classification of Diseases (ICD-10) system in the United States. Under this system, death from food-related anaphylaxis is recorded as a specific cause of death (E. Elliott, FDA, personal communication). Work is underway to define a baseline from 1999 and 2000 data. However, it is not known to what extent the new code for food-related anaphylactic death has been used since the introduction of ICD-10. We included this study in our tally of ongoing projects (Table 5) because CDC staff is reported to be working on it. However, CDC does not have funding specifically devoted to supporting this analysis and therefore CDC is listed as contributing no funding to food allergy research (Table 1).

National Institute of Occupational Safety and Health (NIOSH): NIOSH, another institute within the CDC, was not funding any food allergy research in the third quarter of 2001 when this analysis was conducted. The only project of any relevance was a pilot study of asthma in bakers (Ray Biagini, NIOSH, personal communication). However, the project was excluded because it did not fit the definition of food allergy research. Therefore, at this time, NIOSH does not fund any food allergy research.

United States Department of Agriculture (USDA):

One of the mission areas of the United States Department of Agriculture (USDA) is research, education, and economics, which includes four USDA agencies: the Agricultural Research Service (ARS), the Cooperative State Research, Education, and Extension Service (CSREES), the Economic Research Service (ERS), and the National Agricultural Statistics Service (NASS). According to the CRIS database, USDA had five ongoing research projects in the third quarter of 2001 related to food allergy. A sixth project, identified through the CRIS database, is financed by a state. Of the five projects, two are intramural studies at the ARS and three are grants distributed through CSREES in Alabama, Florida, and Nebraska (Table 5).[6]

6. Since the time of our analysis, USDA funded one additional project, a study directed to the development of an animal model for food allergy, which is funded at $784,000 for thirty-six months. It is not included in our tables or tabulations.

Agricultural Research Service (ARS): ARS is the main in-house research agency at the USDA. ARS employs two thousand scientists, involved in twelve hundred research projects (USDA 2001). The two ARS food allergy projects (Table 5, ID=44, 45) focus on the effects of curing and roasting on peanut allergenicity. In addition to these two studies, the Food Survey Research Group (FSRG) of ARS, has asked questions about food allergy in its nationally representative surveys on food consumption, the Continuing Survey of Food Intakes by Individuals (CSFII) for 1998 (children only) and for CSFII 1994-96 surveys (persons of all ages).[7] Although the data was collected, like the food allergy data collected through NHANES, there are no plans for analysis at this time. Therefore, we did not include this project in our tallies (J. Goldman, FSRG, personal communication). The funding for ARS food allergy research was not available.

Cooperative State Research, Education, and Extension Service (CSREES): CSREES provides grants to institutions to perform research in agriculture and food sciences. CSREES funds three food allergy-related grants. One is funded under the auspices of the National Research Initiative Competitive Grants Program (NRI), an office of CSREES focused on funding projects "in biological, environmental, physical, and social sciences relevant to agriculture, food, and the environment on a peer-reviewed, competitive basis." (One of NRI's priority areas is "Nutrition, Food Safety and Health".) The two other food allergy related projects at CSREES are Multistate Hatch programs and Special Grants.

Of the projects listed at CSREES (including the state-funded one), two projects (ID=46, 47) seek to modify, either by genetic engineering or by traditional breeding, peanut plants to reduce their allergenicity. S. K. Kathe and K. H. Rouke (ID=48) seek to identify and characterize almond and walnut allergens, and examine the effects of processing on those allergens. Finally, investigators are analyzing various food allergens and the allergenic risk posed by biotechnology (ID=49). CSREES invests $587,116 for these research efforts. The funding level for the state funded project (OCI or other cooperating institution) was not available.

United States Environmental Protection Agency (EPA):

The EPA has not traditionally been concerned with food allergies; the agency regulates pesticides, and not natural constituents of plants. However, genetically modified plants have been engineered to produce protein toxins that act as pesticides. As a consequence, the agency has found itself regulating potential food allergens. On StarLink and generally on potentially allergenic proteins,

7. The surveys are going to be integrated into NCHS's National Health and Nutrition Examination Survey (DHHS 2001).

the agency has sought the advice of allergists through its Scientific Advisory Panels (EPA 2000a; EPA 2000b; EPA 2000c; EPA 2000d).

Office of Research and Development (ORD): ORD is the research division of the EPA. Because EPA research is not included in databases, the investigators examined the list of Science to Achieve Results (STAR) grants (http://es.epa.gov/ncer/rfa/) and contacted the chief of the Immunotoxicology Branch of ORD's National Health and Environmental Effects Research Laboratories (NHEERL). We identified no STAR grants or other projects focused on food allergy. A postdoctoral project to develop an animal model of food allergy (ETD-06/05/01-35) was advertised at the time of our analysis, but was not funded. Therefore EPA had no funding for food allergy research in the third quarter of 2001.

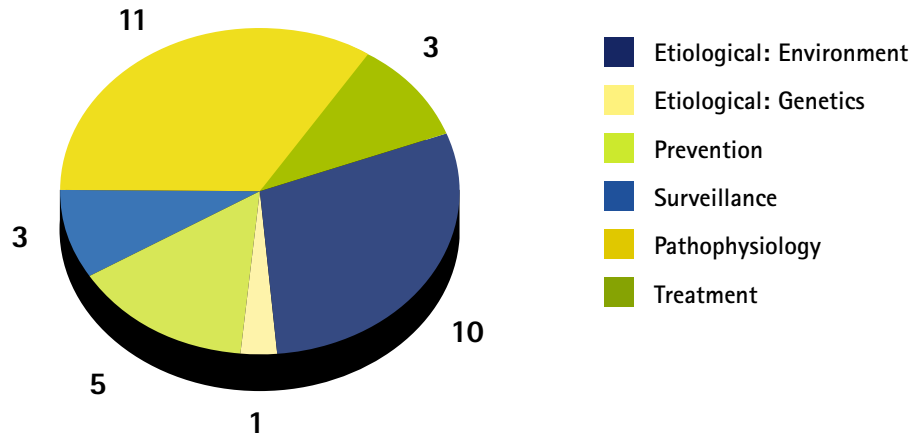
ANALYSIS OF RESEARCH

Classification by Research Goals

The thirty-three food allergy research studies identified in this analysis were examined to determine the goal of each research project. Following Locke, Lucco, and Goldman (2000), research was classified into six categories: etiological (pertaining to the environment), etiological (pertaining to genetics) preventive, surveillance, pathophysiology and treatment **(Figure 1)**. Almost half (n=14) of the projects are devoted either to pathophysiology (n=11) or are treatment related (n=3). A significant share of the projects are devoted to environmental causation (etiological) (n=10). However, these are not environmental epidemiological studies, but mostly studies of molecular determinants of food allergy. Genetic causes are explored in a single study, whereas only three studies address surveillance. Five studies were categorized as prevention, with two funded by the USDA that propose to reduce the allergenic potential of peanuts.

Allergens and their modifications – the "environmental" component of food allergy – are the main focus of the etiological studies. Two studies (Table 5, ID=44, 45) address the effects of processing on allergenicity, three (ID= 25, 26, 41) concern the identification of properties that make foods or proteins allergenic; and two studies address both aspects (ID=48, 49). Another study tries to combine and analyze the information on allergens from published sources (ID=40). Of interest, three of these etiological studies also aim to develop methods for the immunodetection of allergens. In all, six studies seek to identify the molecular determinants of allergenicity, while the effects of processing on allergens are being studied only for peanut allergens. Three studies focus on identifying food allergens or developing simple allergen detection methods. One study is using an epidemiological approach to explore causation of food allergy. One study is investigating the role of heredity in food allergy etiology ("Genetic basis of peanut allergy"). It is unlikely that a single study may be sufficient to explore this aspect of food allergy causation.

FIGURE 1 Research Goals of Federal Food Allergy Research



Federally funded research projects in food allergy by goals of research, including etiological (environmental or genetics), prevention, surveillance, pathophysiology and treatment.

There is little research related to prevention of food allergy. Some studies attempt risk factor reduction or therapeutic strategies that have preventive elements. One study (ID=3) aims at preventing asthma symptoms through diet modification of food allergy/asthmatic children. A second (ID=29) aims to understand whether a specific therapeutic (anti-IgE) approach may prevent the progression from food allergy to asthma. Two studies (ID=46, 47) attempt to lay the foundations of prevention of food allergy through plant breeding. One study attempts to assess whether the elimination of a single allergen makes a plant significantly less capable of sensitizing people (ID=49). In summary, it seems that very few studies are underway to develop prevention strategies against onset or worsening of food allergy; surprisingly, no study attempts to test anaphylaxis prevention strategies. Only three studies aim to test or develop foods of reduced allergenicity despite the potential that biotechnology offers to make progress on this goal.

Surveillance appears to be a neglected area of food allergy research with only three surveillance studies identified. "Natural history of peanut allergy" (ID=28) is documenting the persistence of food allergy into adulthood. Another, "Detection of human antibodies against the recombinant food protein, Cry9C" (ID=43), develops the methodology for the investigation of the alleged outbreak of StarLink corn allergy.[8] Finally, "Healthy People 2010: objective 10.4" (ID=50) is an ongo-

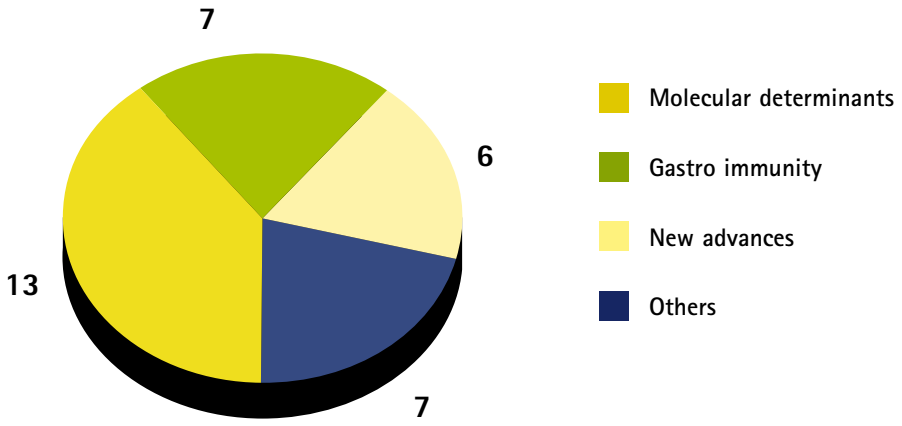
8. The investigation was negative.

ing effort to track food allergy related anaphylactic deaths. Therefore, federal efforts to identify new forms of food allergy and monitor their trends in the population are almost non-existent. While the mortality data collected through Healthy People 2010 tracks an important aspect of food allergy, this alone is insufficient to understand the epidemiology of the disease or how it may be changing over time. We note that two surveillance programs (CDC NHANES III and USDA CSFII) have collected but not analyzed population data on food allergy in the United States.

Classification by Important Research Objectives

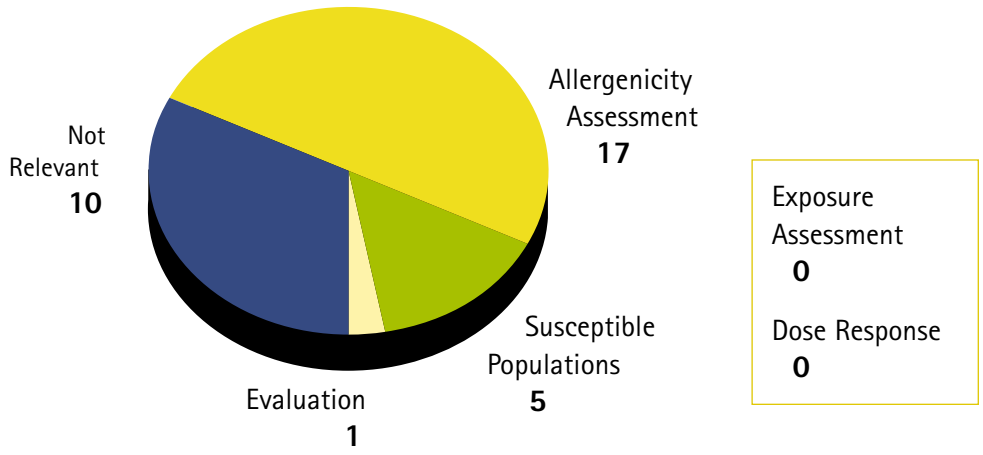
In 1997, a group of leading scientists formed a consensus on important research objectives for food allergy. Plaut described these priorities (1997). Figure 2 shows how studies identified in this analysis fit within these priority areas. The largest category, molecular determinants, includes thirteen studies: threeo funded by the NIH, six by the USDA, and four by the FDA. This finding underscores the role of other agencies, although not purely research-oriented, in ensuring advances in food allergy research. Six studies address the "new leads" identified in Plaut (1997). However, they fall short of addressing some of the issues that the consensus group identified

FIGURE 2 Federal Emphasis on Important Research Objectives



Federally funded research projects in food allergy by research objectives, based on research priorities described by Plaut (1997).

FIGURE 3 **Relevance of Federal Food Allergy Research to Biotechnology Regulatory Assessment**



Federally funded research projects in food allergy by area of relevance to biotechnology

(specifically, histamine-releasing factor (HRF) in food allergy and the role of negative signal transduction in modulating allergic reactions). Gastrointestinal immunity is the subject of only seven studies. In addition, seven studies address issues not prioritized in Plaut (1997); NIH funds eight of these.

Classification by Relevance to Biotechnology Regulatory Assessment

The majority of studies (twenty-three) have the potential to produce information that can inform regulatory policy for biotechnology. Seventeen have the potential to yield results usable for allergenicity assessment, five studies may yield information on susceptible subpopulations, and one study may be useful to evaluate the consequences of potential new allergens **(Figure 3)**. No study addresses dose response or exposure assessment.

Only four of the seventeen projects assigned to Allergenicity Assessment (AA) include research explicitly planned for allergenicity assessment. However, the other studies do address questions that potentially could improve the AA process. For example, a few of the projects may contribute to the development of a predictive animal model for use in allergenicity assessment. Another com-

ponent of allergenicity assessment is the comparison of entire protein sequences and of specific allergic epitopes (i.e., the portion of proteins actually recognized by the immune system) (Metcalfe 1996). Sequence homology between a new protein and a database of known allergens (or allergic epitopes) may help identify potentially allergenic proteins. Several studies plan to contribute new epitope sequences that can contribute to such an allergic epitope database. Prediction of allergenicity is also based on in vitro testing of proteins to determine if they possess biochemical properties similar to those of known allergens. Developing a comprehensive understanding of the biochemical properties of allergens may be important for this purpose. Along this line of inquiry, one study assesses the validity of tests of digestive degradation (Table 5, ID=41); a second (ID=25) examines differential processing of conventional antigens and allergens by antigen presenting cells. A new study addresses the development of animal models for food allergy assessment.

The identification of susceptible populations is also important to protect the whole public from new allergens, including sensitive subpopulations. This can be achieved either by raising standards for the whole population to a level protective of the sensitive subpopulations, or by measures of protection directed at the susceptible populations (e.g., labeling and education). However, such measures cannot be taken if information on susceptibility is not available. Therefore, studies are important if they show that some people are at increased risk of food allergy for genetic reasons (Table 5, ID=24) or because they have other allergic conditions such as atopic dermatitis (ID=18) or asthma (ID=3, 27). Finally, collection of mortality data may also be important to identify segments of the population that are at elevated risk (ID=50).

As part of the risk evaluation process, it is important to find out whether regulatory decisions have in fact protected the public. One of the activities useful for this purpose is the identification of individuals who are reactive to new allergens. Only the study that developed the methods to investigate alleged StarLink allergies fits into the evaluation category (ID=43). Therefore, it seems that little investment is made into the monitoring of adverse outcomes following the introduction of a novel food to the food supply.

The FDA and the EPA have direct regulatory oversight of new, potentially allergenic foods; the CDC cooperates with the FDA on food safety by investigating foodborne disease outbreaks; the USDA regulates genetically modified plants, although it is not concerned with human health effects (NRC 2000). Of the eighteen studies that are relevant to improving the process of Allergenicity Assessment, eight are NIH-funded (35 percent of NIH food allergy studies), six USDA-funded (100 percent of USDA studies), and four are FDA intramural projects (100 percent of FDA studies). As might be expected, the FDA has concentrated its food allergy research efforts in this area, while the NIH has a large proportion of projects that are not relevant to regulation. The results of USDA's projects are also relevant to allergenicity assessment. ■

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