

Functional Foods: Opportunities and Challenges

While food has long been used to improve health, our knowledge of the relationship between food components and health is now being used to improve food. Strictly speaking, all food is functional, in that it provides energy and nutrients necessary for survival. But the term “functional food” in use today conveys health benefits that extend far beyond mere survival. Food and nutrition science has moved from identifying and correcting nutritional deficiencies to designing foods that promote optimal health and reduce the risk of disease.

The costly and complex process of translating these scientific advances and nutritional innovations into consumer products is not without pitfalls. Sound science must underlie the development, marketing and regulation of these new functional foods to protect and inform consumers. Regulatory policies must ensure the safety and efficacy of products and the accuracy of their marketing claims.

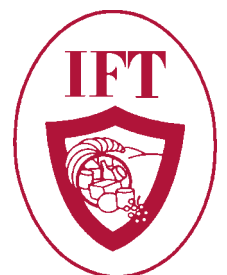
To advance the scientific perspective on these issues, the Institute of Food Technologists (IFT), the 26,000-member

non-profit society for food science and technology, convened a panel of internationally renowned experts to review the science related to functional foods and the regulatory environment for developing and marketing such products.

This IFT Expert Report contains insight from the extensive deliberations of this multidisciplinary panel. As such, it joins two previous IFT Expert Reports—Emerging Microbiological Food Safety Issues: Implications for Control in the 21st Century and Biotechnology and Foods—and an authoritative report, Managing Food Safety: Use of Performance Standards and Other Criteria in Food Inspection Systems. The IFT Office of Science, Communications, and Government Relations coordinated the development of these publications as part of its mission to promote regulatory policies that are based on sound science.

This Expert Report provides a comprehensive review of functional foods that emphasizes the importance of functional foods, summarizes the applicable U.S. laws and regulations, and presents scientifically based guidance for demonstrating both safety and efficacy. The report recommends approaches for improving the regulatory framework to better address evolving science and food composition. In addition, the report identifies potential incentives to expand the availability of new products and facilitate consumer understanding of the benefits of functional foods.

Founded in 1939, the Institute of Food Technologists is an international not-for-profit scientific society with 26,000 members working in food science, technology, and related professions in the food industry, academia, and government. As the society for food science and technology, IFT brings sound science to the public discussion of food issues.



IFT Expert Report Panelists

IFT is deeply grateful to the Expert Report panelists for the time and effort that each of them expended on this project, bringing their expertise and insight into the state-of-the-science on the numerous topics addressed in the report. Panelists traveled to Chicago to participate in full-day meetings and devoted considerable additional time to drafting the report, participating in conference calls to discuss drafts, and reviewing the drafts. IFT sincerely appreciates these experts' invaluable dedication to furthering the understanding of the opportunities and challenges posed by functional food development.

The participants on the Expert Panel were chosen based on their scientific, medical, and legal expertise. Their contributions represent their individual scientific perspective and do not represent the perspective of their employer.

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Definitions

The first step in a comprehensive review of functional foods is to define what exactly is included. Similarly, any discussion of bioactive food components must first begin by defining the term “nutrients.”

Functional Foods

The Expert Panel, for purposes of this report, defines “functional foods” as foods and food components that provide a health benefit beyond basic nutrition (for the intended population). Examples may include conventional foods; fortified, enriched or enhanced foods; and dietary supplements. These substances provide essential nutrients often beyond quantities necessary for normal maintenance, growth, and development, and/or other biologically active components that impart health benefits or desirable physiological effects.

Nutrients

For purposes of this Expert Report, nutrients are defined as traditional vitamins, minerals, essential fatty acids for which recommended intakes have been established and other components that include phytonutrients or bioactives present in foods for which a physical or physiological effect has been scientifically documented or for which a substantial body of evidence exists for a plausible mechanism, but for which a recommended intake and function have not been definitively established.

Introduction

The combination of consumer desires, advances in food technology, and new evidence-based science linking diet to disease and disease prevention has created an unprecedented opportunity to address public health issues through diet and lifestyle. Widespread interest in select foods that might promote health has resulted in the use of the term “functional foods.” Although most foods can be considered “functional,” in the context of this report the term is reserved for foods and food components that have been demonstrated to provide specific health benefits beyond basic nutrition (see definition on page 6). The term functional food is thus arbitrary, but it is nonetheless useful since it will convey to the consumer both the unique characteristics of the food and the associated health benefits.

The members of the Institute of Food Technologists (IFT) recognize that the foods already on the market represent a small fraction of the potential for functional foods. Today’s science and technology can be used to provide many additional functional foods, and future scientific and technological advances promise an even greater range of health benefits for consumers. Functional foods can provide health benefits by reducing the risk of chronic disease and enhancing the ability to manage chronic disease, thus improving the quality of life. Functional foods also can promote growth and development and enhance performance.

IFT prepared this Expert Report to provide a detailed, state-of-the-art review of the development of functional foods, including the products, the science, and the possibilities. (The report discusses examples of functional foods, however it does not provide a comprehensive review of all functional foods.) The report also emphasizes the importance of functional foods, provides scientifically based guidance for demonstrating both safety and efficacy, and provides a comprehensive summary of the applicable U.S. laws and regulations. The report proposes solutions to current impediments to functional food development, including limitations in the existing regulatory framework and the need for appropriate incentives to expand the availability of new products.

Unlocking the Secrets of Functional Food Components

Food technology and improved nutrition have played critical roles in the dramatic increase in life expectancy over

the past 200 years, but the impact of diet on health is much broader than basic nutrition. A growing body of evidence documents positive health benefits from food components not considered nutrients in the traditional definition. Scientific advances have allowed researchers to better characterize the biological basis of disease states, understand the metabolism of food at the cellular level, and identify the role of bioactive components in food and assess their impact on metabolic processes. New powerful analytical tools can enable scientists to unlock the biological functions of vast numbers of food components and their role in disease prevention and health promotion.

Functional foods can take many forms. Some may be conventional foods with bioactive components that can now be identified and linked to positive health outcomes. Some may be fortified or enhanced foods, specifically created to reduce disease risk for a certain group of people. Consumers can already select from a wide spectrum of foods that contain functional components either inherently (e.g., soy protein, cranberries) or via fortification (e.g., folate-fortified foods). Health benefits may result from increasing the consumption of substances already part of an individual’s diet or from adding new substances to an individual’s diet.

As additional bioactive components are identified, the opportunities for developing functional foods will be broad (O’Donnell, 2003). Foods that naturally provide a bioactive substance may be enhanced to increase the level present in the food (e.g., eggs with increased levels of omega-3 fatty acids). Alternately, foods that do not naturally contain a substance can be fortified to provide consumers with a broader selection of food sources for a particular component and its health benefit (e.g., calcium-fortified orange juice).

Areas for research include better understanding the role and optimal levels of traditional nutrients for specific segments of the population, as well as identifying bioactive substances present in foods and establishing optimal levels. Early nutrition research focused on the range of vitamin and mineral intakes necessary to prevent frank deficiencies. Now, researchers are investigating the optimum intake levels for traditional nutrients and the differences for various subpopulations. Understanding the role of nutrients at the molecular level will result in even more specific recommended dietary allowances for different population subgroups. Similar research is needed to identify the role of other bioactive food components, an area of research that is still in its infancy. Only recently, several government agencies have begun developing a standard definition for “bioactive” food components (HHS/OS/OPHS, 2004).

Research has proven that food and isolated food components can reduce the risk of disease, from the effect of vitamin A from eggs on blindness to the effect of zinc from high-protein foods on the immune system. Some examples

of foods that may be considered functional foods include calcium-fortified orange juice, phytosterol/stanol-fortified spreads and juices, folate-enriched foods, soluble oat fiber, cranberry, and soy (see Table 1).

Research currently underway at academic, industry and government facilities will reveal how a myriad of substances can be used as functional food components. Although additional research is necessary to validate efficacy and establish appropriate dietary levels, researchers have identified functional food components that may improve memory, reduce arthritis, reduce cardiovascular disease and provide other benefits typically associated with drugs.

In addition, new technologies will provide opportunities to produce bioactive food components from nontraditional sources. For example, Abbadi et al. (2004) developed transgenic plant oils enriched with very long chain polyunsaturated fatty acids. Other research has produced stearidonic acid (a precursor for eicosapentaenoic acid) in canola seeds to provide another source of omega-3 fatty acids in the diet (James et al., 2003; Ursin, 2003).

Emerging science requires that we broaden our frame of reference to take full advantage of these new discoveries. Foods may be developed to promote the expression of specific metabolites, reducing or preventing common diseases that afflict consumers with a specific genotype. Consumers might select functional foods and tailor their diets to meet changing health goals and different requirements at different ages. Future benefits might include functional foods for increased energy, mental alertness, and better sleep.

Shifting the Paradigm for Health and Wellness

A growing number of consumers perceive the ability to control their health by improving their present health and/or hedging against aging and future disease. These consumers create a demand for food products with enhanced characteristics and associated health benefits. In one study, 93% of consumers believed certain foods have health benefits that may reduce the risk of disease or other health concerns. In addition, 85% expressed interest in learning more about the health benefits offered by functional foods (IFIC, 2002).

Using foods to provide benefits beyond preventing

deficiency diseases is a logical extension of traditional nutritional interventions. Nonetheless, such an extension requires changes in not only the foods themselves, but also their regulation and marketing—truly a paradigm shift.

Creating a scientifically valid distinction between food and medicine has never been easy. Centuries ago, Hippocrates advised, “Let food be thy medicine and medicine be thy food.” Early nutrition research resulted in cures for numerous widespread deficiency-based diseases. Recent scientific advances have further blurred the line between food and medicine, as scientists identify bioactive food components that can reduce the risk of chronic disease, improve quality of life, and promote proper growth and development.

The Traditional Paradigm

Traditional fortification of foods with vitamins and minerals has been accepted by consumers and regulators, but consumers should recognize the clear distinction between the use and purpose of foods vs. drugs (see Fig. 1).

Food has traditionally been viewed as a means of providing normal growth and development. Regulatory policies were established to replace nutrients lost during processing and, in some cases, to prevent nutrient deficiencies in the population. Federal policies have generally required that other diseases be treated and managed through the use of drugs.

A New Paradigm

A new self-care paradigm (adapted from Clydesdale, 1998) recognizes that foods can provide health benefits that can co-exist with traditional medical approaches to disease treatment. Science has clearly demonstrated additional dietary roles in reducing disease risk, and consumers have learned that food has a greater impact on health than previously known. At the same time, consumers recognize problems with the current healthcare system, perceiving that it is often expensive, time-constrained, and impersonal.

Functional foods fit into a continuum that ranges from health maintenance/promotion to disease treatment (see Fig. 2). On one end of the continuum are public health programs aimed at reducing disease risk in a large segment of the population through self-directed lifestyle changes. The other end of the continuum is individualized treatment of disease by health care professionals using drugs and other medical interventions. Although the health professional involvement is low in self-directed treatment relative to individualized treatment, an important educational component remains. New functional foods will continue to expand the continuum, providing additional options for consumers. There is a role for all aspects of this paradigm in our health care

Table 1. Examples of Functional Food Components Currently Marketed

Functional Component	Health Benefits	U.S. Regulatory Status of Claims
Soluble oat fiber	Coronary heart disease	FDA approved health claim
Soy protein	Coronary heart disease	FDA approved health claim
Phytosterol/stanol esters	Coronary heart disease	FDA approved health claim (interim final rule)
Calcium	Osteoporosis	FDA approved health claim
Folate-enriched foods	Neural tube defects	FDA approved health claim

Fig. 1. Benefits and Risks of Foods vs. Drugs

Food and Food Components	Drugs
Energy/nutrition/necessary for life	Treatment of disease
Life long use and benefits	Immediate effect
All populations	Target population
Safe ^a	Benefit > risk
Consumer selects	Health provider prescribes

Adapted from Yetley, 1996.

^a Safe when consumed as a food, but with a potential increase in risk as the component levels increase. Safety evaluation will be conducted to identify the limits.

system. Functional foods should be integral components of established public health programs to reduce the risk of specific diseases (Clydesdale, 1998).

Treatment and prevention of coronary heart disease (CHD) provides an example of this paradigm shift. In the past, recommendations for treating hypercholesterolemia, one of the risk factors for CHD, included dietary and lifestyle interventions along with medication. The dietary and lifestyle interventions included reducing intake of saturated fat and cholesterol, quitting smoking, increasing regular physical activity, and maintaining a healthy body weight (NCEP, 1988, 1993). These recommendations, often in conjunction with medication, have been effective strategies for managing heart disease.

The most recent clinical guidelines for treatment of coronary heart disease include therapeutic dietary options for reducing low density lipoproteins (LDL) by consuming specific foods, such as those that contain plant stanols/sterols, increasing intake of soluble fiber, and reducing intake of trans fatty acids (NCEP, 2001). Several food components currently under study may provide additional dietary options in the prevention and treatment of CHD.

Tailoring Diets for Special Needs

Functional foods can address many consumer needs within the new paradigm when used as part of a diet tailored to address the special health needs of a specific group of consumers. In addition to those with needs because of chronic medical conditions, other groups with special needs include women of childbearing age, adolescent girls and boys, athletes, military personnel, and the elderly.

For example, improving the health of the elderly in cost effective and consumer-acceptable ways will become even more urgent as the population of individuals 65 years of age and over increases by approximately 50% during the next 27 years (see Fig. 3).

The Institute of Medicine (IOM, 2000) reported that poor

nutritional status is a major issue for older citizens and that at least four health conditions (under nutrition, cardiovascular disease, diabetes, and osteoporosis) would benefit from nutritional intervention in either “preventative or treatment modes.” Some functional foods are already available for each of these purposes, but more are needed. Many elderly individuals may benefit by expanding their use of functional foods and supplements, particularly where new research can guide their selection of those foods to meet specific needs.

It would be unreasonable to expect functional foods to address all of the elderly’s medical needs, but functional foods can improve health and wellness, minimize costs, and provide consumers with greater control.

Encouraging the Development of Functional Foods

As research provides clear evidence of relationships between dietary components and health benefits, the challenge has just begun. Scientific, regulatory, and business frameworks must be in place to evaluate the data for efficacy and safety, ensure effective regulatory oversight, communicate the findings to consumers, and provide incentives that encourage research and development of these novel food products.

This report recommends modifications to the existing efficacy and safety evaluation process to ensure a sound scientific underpinning for each proposed functional food, while providing clear information to consumers. Corresponding improvements in the regulatory oversight of new functional components also are proposed. These changes must be implemented now to protect consumer confidence in the safety of the food supply and to encourage the food industry to invest in the development of new functional foods. Science is moving rapidly; industry and government must also move rapidly to ensure that the results are translated into benefits for the consumer. The functional foods currently available represent only a fraction of the potential opportunities for consumers to manage health through diet.

Traditional definitions and arbitrary distinctions between food and medicine should not prevent consumer access to knowledge about the benefits of incorporating functional foods into their diets. Likewise, the framework for provid-

Fig. 2. Role of Functional Foods in Health Care Continuum

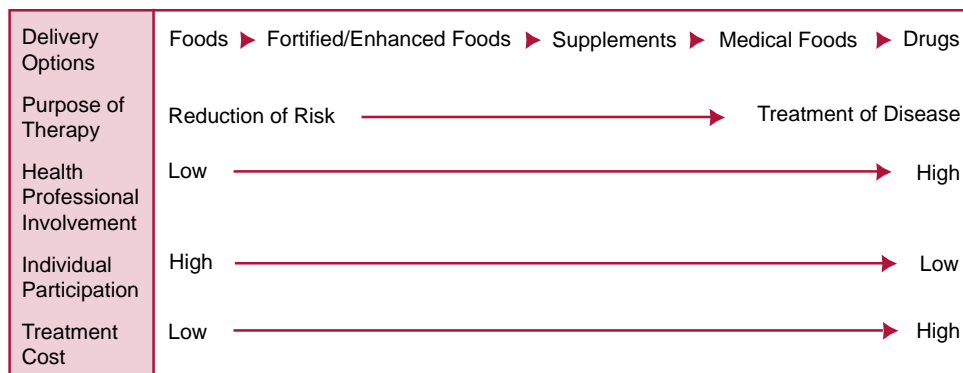
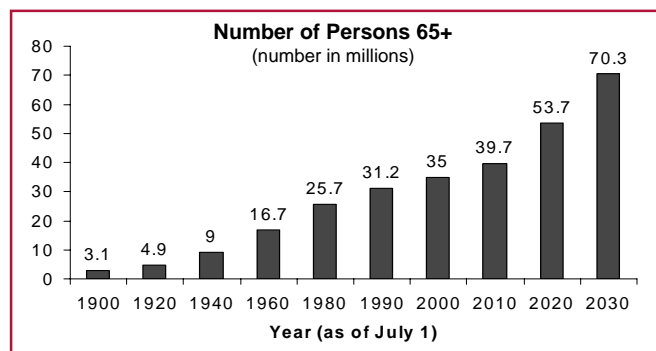


Fig. 3. Projected Increase in Number of Elderly Individuals (AOA, 2002)



ing strong regulatory oversight should not present unnecessary barriers to the development and marketing of functional foods. Where existing terminology and regulatory frameworks are inadequate to address the full scope of benefits and opportunities for functional foods, the terminology and

the frameworks must be modified.

Developing a new functional food is an expensive process. Food companies have traditionally funded research for new food product formulations but for functional foods, the stakes are higher—for both food companies and consumers. Government investment in basic and applied research will promote the development of functional foods, but additional incentives are needed to reward private companies that pioneer new health claims. The research required for a functional food to meet scientific standards for efficacy and safety is a substantial investment, but currently the return on that investment is not exclusive to the company that conducted the research and developed the initial regulatory petition. As soon as the health claim is adequately documented, competing companies can use the claim. Incentives, such as a period of exclusivity or tax incentives, would encourage food companies to pursue functional food development by ensuring a profitable return on successful products.

The Intersection of Food and Genes

Understanding of human dietary requirements results from developments in many scientific disciplines, including food science, nutrition, chemistry, biochemistry, physiology, and genetics. New research in proteomics, nutrigenomics, metabolomics, and other disciplines may help identify the biological basis by which food components promote health and wellness. Continuing and accelerating this research will reveal the effects of nutrients on the molecular-level processes in the body and document the variable effects of nutrients under different conditions.

New Disciplines

Nutrigenomics, proteomics and metabolomics are three new disciplines that will contribute to the rapid development of functional foods. Bioinformatics is a new tool that uses computer database technology to integrate data from multiple, and sometimes disparate, disciplines. Already these disciplines and tools have improved our understanding of food science and human nutrition. Discoveries in genetics make it possible to understand the effects of nutrients in processes at the molecular level in the body and also the variable effects of dietary components on each individual.

The scientific and technological discipline named nutrigenomics relies heavily on well established science and technology from the fields of genomics, proteomics, metabolomics, food science, and nutrition (see Table 2).

Briefly, nutrigenomics describes how dietary components affect the protein profile of an individual. Proteomics describes how that altered protein profile affects the biological systems of the individual, and metabolomics describes the cellular response to the changes. The metabolite and gene expression patterns discovered with emerging bioinformatics tools may be used to monitor sequential metabolic changes in response to dietary components in functional foods, facilitating evaluation of the safety and efficacy of these components. Each of these disciplines is described in greater detail below.

Nutrigenomics

For the purposes of this discussion, nutrigenomics is defined as the interaction of dietary components with genes. The dietary components of interest can be essential nutrients (e.g., vitamins, minerals, fatty acids), other bioactive substances (e.g., phytochemicals) or metabolites of food components (e.g., retinoic acid, eicosanoids). On the one hand, nutrigenomics represents a logical extension of

biotechnology, molecular medicine, and pharmacogenomics; on the other hand, it represents a revolution in how nutrition and diets are viewed in relation to health (Fogg-Johnson and Merolli, 2000; Patterson et al., 1999). Saubert et al. (1973) were among the early, dedicated pioneers who established analytical methods to assess the nutritional status of humans, using biological fluids (notably urine and plasma) and red and white blood cells. Additional laboratory tests for the assessment of nutritional status are needed, such as the ability to measure osteocalcin (an indicator of osteoblastic/orthoclastic activity) instead of relying on measurements of plasma Ca to determine calcium status. Ideally, functional assessment of nutritional status would use non-invasive biofluids and emerging highly sensitive, analytical technologies.

Proteomics

Proteomics is the study of the full set of proteins encoded and expressed by a genome. Proteomics identifies the large number of proteins in the organism, maps their interactions and analyzes the proteins' biologic activities. Zhu et al. (2003) provide a comprehensive review of available analytical techniques and their use in proteomics.

Metabolomics

Metabolomics (or metabonomics) is metabolite profiling, measuring the real outcome of the potential changes suggested by genomics and proteomics. Metabolomics investigates regulation and metabolic fluxes in individual cells or cell types. Metabonomics combines the power of high-resolution nuclear magnetic resonance with statistical data analysis of *in vivo* metabolite patterns. This technique enables rapid screening for xenobiotic toxicity, disease state, drug efficiency, nutritional status and even gene function in the "whole" organism. (Nicholson et al., 2002). This emerging investigative approach is being used to assess the adequacy and safety of xenobiotics, pharmaceutical agents, nutrients and functional phytochemicals (Khandurina and Guttman, 2002; Reo, 2002; Weckwerth, 2003).

Future Developments

Diet represents one of the key environmental factors to which our genes are exposed, from conception throughout life. Gene expression results in production of proteins that function in myriad ways within the human body, serving as enzymes, oxygen transporters, hormones, and building blocks for cells throughout the body. Simply put, gene expression governs our existence. Nutrients, in turn, govern the concentration of different proteins in different organs by functioning as regulators of gene transcription and translation, nuclear RNA (ribonucleic acid) processing, messenger RNA (mRNA) stability, and mRNA degradation. The

Table 2. Terminology and Disciplines Pertinent to Applications of Genetic Research to Nutrition and Health

Term	Definition and Function
Gene	A gene is a DNA (deoxyribonucleic acid) segment that contributes to phenotype/function as defined by HUGO (Human Genome Organization) (White et al., 1997).
Genome	Life is specified by genomes. Every organism, including humans, has a genome that contains all the biological information needed to build and maintain a living example of that organism. The biological information contained in a genome is encoded in its DNA and divided into discrete units called genes. Genes code for proteins that attach to the genome at the appropriate positions and switch on a series of reactions called gene expression.
Genomics	The characterization and study of whole genomes with respect to the DNA sequence, and the arrangement and function of genes. Further specified as: structural genomics (mapping and sequencing genes) and functional genomics (understanding the functions of genes, the proteins made as a result of gene activation [expression], and the interactions of those proteins).
Genotype	The genetic constitution of an organism, as distinguished from its physical appearance (its phenotype). The genetic identity of an individual that does not show as outward characteristics.
Phenotype	The physical characteristics or observable traits of an organism, e.g., hair color, weight, or the presence or absence of a disease. Phenotypic traits are not necessarily genetic.
Single Nucleotide Polymorphism (SNP) (pronounced "snip")	Heritable, individual variations that occur in one nucleotide such that DNA and gene sequences, and ultimately proteins produced by those genes, vary from one person to the next. Differences in proteins are minor, usually on the order of one amino acid; however, effects on protein function may be significant and cause or contribute to individual differences in response to environment, such as diet and drugs. A small genetic change, or variation, that can occur within a person's DNA sequence. The genetic code is specified by the four nucleotide "letters": A (adenine), C (cytosine), T (thymine), and G (guanine). SNP variation occurs when a single nucleotide, such as an A, replaces one of the other three nucleotide letters, C, G, or T.
Polymorphism	An alternate form of a gene present in >1% of the population.
Proteomics	The study of the full set of proteins encoded and expressed by a genome, from healthy and diseased tissues. Further specified as (INGEN, 2001): structural proteomics (identifying proteins by analyzing amino acid sequences); molecular proteomics (studying the interactions of proteins with other proteins and cellular components); and chemical proteomics (studying the interaction of proteins with chemicals, such as drugs, nutrients and toxins).
Metabonomics or Metabolomics	Metabolite profiling measures the real outcome of the potential changes suggested by genomics and proteomics. It describes the integrated biochemical status, dynamics, interactions, and regulation of whole systems or organisms at a molecular level. Systems biology approaches present a different and broader perspective from the discrete, relatively static measurements of the past. As such, they offer new understanding of disease processes and targets and the beneficial and adverse effects of drugs; but they also bring new challenges. Exploitation of patterns rather than single indicators and the dynamic nature of metabonomics end-points suggest a dose-response continuum and perhaps challenge both industry and regulators with the obsolescence of the crude no-effect dose/effect dose concept. Characterization of individual amenability to therapy and susceptibility to toxicity ("pharmacometabonomics") has economic and ethical implications. These opportunities and challenges will be explored in the context of the present and future roles of metabonomics in drug development.
Bioinformatics	The field of science in which biology, computer science, and information technology merge to form a single discipline based on creation and mining of extensive computerized databases of nucleic acid sequences, gene structures, proteins and their function, as well as environmental constituents capable of modifying gene expression. The ultimate goal of the field is to enable the discovery of new biological insights as well as to create a global perspective from which unifying principles in biology can be discerned.
Nutrigenomics	The interaction of dietary components that are nutritive (vitamins, minerals, fatty acids), bioactive (phytochemicals), or metabolites of food components (retinoic acid, eicosanoids) with genes to result in gene expression.

intensity of a dietary signal and the subsequent response can vary with the amount of a food component consumed and the frequency with which it is ingested. The developmental age of the individual also may determine which genes are influenced (Clarke, 2001). Although an exhaustive review of the scientific literature is beyond the scope of this report, Tables 3 and 4 provide an overview.

As summarized in Table 3, research has shown that nutrients affect gene expression and formation of various proteins at discrete points in the processes leading to enzymes, structural proteins, and other chemicals on which life depends. Thus, the amount—and even the form—of nutrients present during gene expression can affect the

synthesis of protein, resulting in less of a protein being produced, production of a less than optimally functional form, or no protein at all. Each of those possibilities exists due to the hereditary form of genes present and whether the genes are normal or contain polymorphisms that affect gene expression.

Studies designed to identify specific effects of diet on phenotypic expression of biochemical components that determine health have resulted in tantalizing suggestions for dietary interventions designed to modify gene expression (see Table 4). Nutrients serve as substrates, cofactors, or coenzymes for metabolic processes that are familiar from traditional nutritional research and epidemiological observa-

Table 3. Gene Expression Processes Leading to Protein Formation and Selected Nutrient Regulators in the Process

Gene Expression Sequence	Nutrient Regulator	Reference
Gene transcription	Fatty acids, glucose, cholesterol, amino acids, zinc, bioactive components	Berger et al., 2002; Brown et al., 2003; Carluccio et al., 2003; Chowanadisai et al., 2004; Iizuka et al., 2004; Jousse et al., 2004; Koo et al., 2001; Stoeckman and Towle, 2002; Uyeda et al., 2002
mRNA processing	Methionine, choline, vitamins B-6 & B-12, fatty acids	Mater et al., 1999; Niculescu and Zeisel, 2002
mRNA stability	Amino acids, vitamin D, calcium	Fafournoux et al., 2000; Slattery et al., 2004
mRNA translation	Glucose, fatty acids, minerals, amino acids, choline, conjugated linoleic acid (CLA)	Brown et al., 2004; Campos et al., 2001; Doering and Danner, 2000; Fafournoux et al., 2000; Hasty et al., 2000; Liu et al., 2000; Niculescu et al., 2004; Redonnet et al., 2002; Slattery et al., 2002
Post-translational modification	Minerals and vitamin cofactors	Bailey and Gregory, 1999; Campbell et al., 1999; Escher and Wahli, 2000
Protein transport to functional location	Vitamins, minerals	Kelleher and Lonnerdal, 2002

tion. New genetic research techniques are finding that nutrients also regulate the genes whose expression leads to enzymes, transporters, and structural elements that comprise the living, functioning organism.

The premise that foods consumed during the first weeks and months of life may have permanent effects on metabolism is not new. In fact, the relationship was first recognized more than 40 years ago (McCance, 1962). Further studies in humans and animals showed permanent effects of early diet on adult metabolism, cognitive function, and body composition through activation or suppression of gene expression, or turning genes “on” or “off” (Barker et al., 1993; Hattersley and Tooke, 1999; Moor and Davies, 2001; Ong and Dunger, 2002). Ample scientific evidence demonstrates that diet is a significant environmental determinant, if not the key determinant, of population or individual genetic expression (Ames et al., 2002; Choi et al., 2000; Clarke, 2001; Deeb et al., 1998; Halushka et al., 1999; Jeanpierre, 1998; Jensen et al., 1999; Krauss, 2000; Lucas, 1998; Rantala et al., 2000; Schwanstecher and Schwanstecher, 2002; Stoll et al., 1999). Those effects can be overt, such as the effects seen in vitamin deficiency diseases, or more subtle and complex, as in the manifestation of type 2 diabetes, predisposition to obesity, and other chronic diseases. For example, epidemiological surveys of adults born after prenatal exposure to famine and biochemical investigations of insulin resistance in low-birth-weight children both show a genetic basis for the observed association between low birth weight and an increased risk of developing

type 2 diabetes later in life. The predisposing genetic changes have been shown to occur *in utero* (Barker, 1997; Goldberg and Prentice, 1994; Langley-Evans et al., 1998).

Although scientists knew such a relationship existed between early diet and gene expression, they were unable to understand how the effect took place. Now, the integration of genomics and nutrition is providing an emerging understanding—at the molecular level—of how diet affects gene expression. This new understanding opens the door for many potential nutritional interventions, both in food composition and in food selection.

The health consequences of the interaction between an individual’s diet and his or her genetic makeup have been repeatedly demonstrat-

ed. In fact, some life-threatening errors of metabolism have been successfully managed with diet modification. For example, galactosemia, a genetic disorder characterized by an inability to convert galactose to glucose, is usually discovered in infants fed milk shortly after birth because milk contains a large quantity of galactose. If not treated, galactosemia can result in cataracts, enlarged liver and spleen, and mental retardation. It is treated by lifelong elimination of milk and other dairy products from the diet. Another example of an inborn error of metabolism, phenylketonuria (PKU) is caused by an enzyme defect in the liver that breaks down phenylalanine. As a result, phenylalanine builds up in the body, causing mental retardation. Although PKU cannot be prevented, if detected early in life, it can be successfully treated by consuming a diet low in phenylalanine.

The Human Genome Project and associated programs have provided the groundwork for scientists to be able to

Table 4. Examples of Nutrient Involvement in Gene Expression and Potential Phenotypic Results

Nutrient Deficiency	Phenotypic Expression	Reference
Folate	Elevated homocysteine (cardiovascular disease), neural tube defects, central nervous system dysfunction	Clarke, 2001; Kolling et al., 2004; Regland et al., 1997; Shields et al., 1999; Susser et al., 1998; Verhoef et al., 1997; Yoo et al., 2000 (Also, Kunugi et al., 1998 and Virgos et al., 1999 for contrasting views)
Fatty acids	Cognitive function (depression), obesity, Inflammation	Covault et al., 2004; Escher and Wahli, 2000; Saugstad, 2001; Takahashi et al., 2002; Vlassara et al., 2002
Vitamin D	Osteoporosis	Chen et al., 2002; Sowers et al., 1999

pursue key questions, such as: What DNA variants underlie disease and health? How does environment interact with genes, subjecting some individuals to intractable obesity, cardiovascular disease or Alzheimer's disease at early ages, while others have a long life with little or no disease?

Genetic factors may confer susceptibility or resistance to a disease and may determine the severity or progression of disease. Since we do not yet know all of the factors involved in these intricate pathways, researchers have found it difficult to develop screening tests for most diseases and disorders. Today this can be solved by studying stretches of DNA that have been found to harbor a single nucleotide polymorphism (SNP) associated with a disease trait, researchers may begin to find relevant genes associated with a disease and variable response to dietary components. It is already possible to identify individuals with an SNP profile that predicts variable cardiovascular health status in response to diets with a particular fat composition (Couture et al., 2000). Defining and understanding the role of genetic factors in disease also will allow researchers to better evaluate the role that non-genetic factors—such as behavior, diet, lifestyle and physical activity—have on disease.

While the SNPs or polymorphisms that appear to be associated with some diseases can be identified, a substantial amount of biological research remains to be completed to unequivocally link, in a cause-effect equation, the phenotypic expression of health or disease in response

to intake of a specific nutrient or bioactive component. Experimental results show that individuals whose genetic makeup contains particular SNPs may respond to dietary components in ways that result in gene expression that leads to disease phenotypes.

The challenges facing nutrigenomics are similar to those encountered in drug development. Many common diseases are not caused by a genetic variation within a single gene. Instead, diseases are caused by complex interactions among multiple genes, in conjunction with environmental and lifestyle factors. Although both environmental and lifestyle factors contribute tremendously to disease risk, their relative contributions and effects are currently difficult to measure and evaluate.

Now that the human genome has been catalogued, the race is on to determine the functional significance of each gene, understand the complex functional networks and control mechanisms, and figure out the role that genotype and environment play in determining the phenotype of an individual. Functional studies to date have largely evaluated one gene at a time. However, to truly understand the biology of processes directed by genes, researchers need to simultaneously study functional interactions, networks, and pathways. With enough data and proper bioinformatics tools, scientists will be able to model the genetic circuitry to identify interventions that can optimize biological outcomes through health and wellness lifestyle choices such as diet.

Current U.S. Legal Standards for Health-Related Claims

In the United States, statutes and regulations have not been implemented specifically for functional foods. Functional foods are regulated under the same statutes as other food and food products. This section discusses the current statutes and regulations governing the different types of labeling claims. The information presented is reflective of policy developments in this area with extensive activity pertaining to dietary supplements. Limitations in the current laws and regulations are noted elsewhere in the report.

Terminology

This section of the report will not mention “functional foods,” “phytofoods,” “vitafoods,” or the like. These are terms that have come into use in the food industry to describe foods that have particular health-related benefits, but they are not terms that are recognized in the Federal Food, Drug, and Cosmetic Act (FDC Act) or in U.S. Food and Drug Administration (FDA) regulations. Just because, in industry parlance, a particular food product might be described as a “functional food” does not mean that that food is subject to any special legal requirements or exemptions; instead, all the general legal principles described in this section would potentially apply. For example, if such a food bears a label claim that comes within the definition of a health claim, the claim must comply with applicable provisions of law concerning health claims.

Threshold Problem: Need to Avoid Drug Status

The FDC Act, Section 201 (g)(1), states in pertinent part:

The term “drug” means ...

(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease ...; and

(C) articles (other than food) intended to affect the structure or any function of the body (21 USC § 321(g)(1)).

Therefore, in general, no claim should be made for a food that represents that it is intended to cure, mitigate, treat, or prevent any disease. Such a claim can cause a food to become subject to regulation as a drug, which would trigger numerous requirements applicable to drugs (including the possibility of a requirement for FDA approval of a new drug application prior to marketing). In most cases, drug status for a food would make it illegal, since, as a putative food, the product almost certainly would not be in compliance with all applicable drug requirements.

The one significant exception is that the Nutrition Labeling and Education Act (NLEA) of 1990 authorizes FDA to allow certain disease-risk-reduction claims, known as “health claims,” to appear in food labeling. On first impression, health claims might appear to risk triggering drug status because they suggest that a food will have a mitigating or preventive effect with respect to a disease. Nevertheless, health claims are exempt from drug status, provided that all of the applicable requirements for each type of claim are met. However, failure to comply with all of the applicable requirements for an approved health claim may cause FDA to assert that the subject food is either a misbranded (misabeled and therefore illegal) food, or a product that is an illegal drug for failure to comply with all applicable drug requirements.

Health Claims

NLEA allows labeling claims for dietary supplements and conventional foods that “characterize the relationship of any substance to a disease or health-related condition” if the claim is first approved by an FDA regulation.

“Health claims” that FDA has approved generally have been claims to the effect that inclusion of a substance in the diet on a regular basis “may help to reduce the risk” of a named disease. Currently, the FDA regulations in 21 CFR §§ 101.72 to 101.83 lay out the requirements for approved health claims regarding calcium and osteoporosis; dietary lipids and cancer; sodium and hypertension; dietary saturated fat and cholesterol and coronary heart disease (CHD); fiber-containing grain products, fruits and vegetables, and cancer; fruits, vegetables and grain-products containing fiber, particularly soluble fiber, and CHD; fruits and vegetables and cancer; folate and neural tube defects; non-cariogenic carbohydrate sweeteners and dental caries; soluble fiber and CHD; soy protein and CHD; and plant sterol/stanol esters and CHD.

Additionally, in 1997 Congress authorized the use of certain health claims for foods and dietary supplements based on an “authoritative statement” by a “scientific body,” as reviewed below.

It is important to note that not all claims about health are health claims: A claim that links a nutrient solely to the normal, healthy structure or function of the human body, e.g., “protein helps build strong and healthy muscles,” is not a health claim under these regulations, and therefore does not require FDA preclearance. (See below for further discussion about the use of such “structure/function claims.”)

One may petition FDA to issue a regulation to approve a health claim, but FDA will issue such a regulation only when it determines, based on the totality of publicly available scientific evidence (including evidence from well designed studies conducted in a manner which is consistent

with generally recognized scientific procedures and principles), that there is significant scientific agreement (SSA)—among experts qualified by scientific training and experience to evaluate such claims—that the claim is supported by such evidence. (See discussion of SSA beginning on page 24.)

Claims Based on Authoritative Statements

The FDA Modernization Act (FDAMA) of 1997 amended the FDC Act to authorize food labeling to include certain health claims without approval by an FDA regulation. Such a health claim must be the subject of a “published ... authoritative statement, which is currently in effect,” issued by a “scientific body of the U.S. Government with official responsibility for public health protection or research directly relating to human nutrition (such as the National Institutes of Health [NIH], the Centers for Disease Control and Prevention) or the National Academy of Sciences [NAS].”¹

At least 120 days prior to using one of these claims, the manufacturer must submit to FDA the exact claim wording, a copy of the “authoritative statement” upon which the claim is premised, and a “balanced representation of the scientific literature” relating to the claim. FDA is the final arbiter about whether such a notified health claim may be used in labeling because FDA may issue a regulation prohibiting or modifying the claim or finding that the requirements to use the claim have not been met. The notified health claims allowed by FDA thus far are claims concerning foods that are a good source of potassium and low in sodium and hypertension and stroke (FDA/CFSAN/ONPLDS, 2000a); diets high in whole grains and CHD and certain cancers (FDA/CFSAN/OFL, 1999); and diets rich in whole grain and other plant foods and low in total fat, saturated fat and cholesterol, and heart disease and certain cancers (FDA/CFSAN/ONPLDS, 2003a). All notified health claims thus far have been based on statements in the NAS report, “Diet and Health: Implications for Reducing Chronic Disease Risk.”

Another general requirement, known as the “jelly bean rule” in 21 CFR § 101.14(c)(6), requires foods (other than dietary supplements) bearing a health claim to contain 10% or more of the reference daily intake (RDI) or daily reference value (DRV) for vitamin A, vitamin C, iron, calcium, protein or fiber per reference amount customarily consumed (RACC) prior to any nutrient addition, unless otherwise

¹ On June 11, 1998, FDA issued “Guidance for Industry: Notification of a Health Claim or Nutrient Content Claim Based on an Authoritative Statement of a Scientific Body” (FDA/CFSAN/OFL, 1998). These guidelines express generally conservative interpretations of the FDAMA provisions that allow a health claim or nutrient content claim to be used without an approving FDA regulation based on an authoritative statement by a scientific body. Among other provisions, the FDA guidance states the view that an authoritative statement should “reflect a consensus within the identified scientific body if published by a subdivision of one of the Federal scientific bodies,” and should “be based on a deliberative review by the scientific body of the scientific evidence.” FDA states, “Not all pronouncements by the designated scientific bodies would meet these criteria.”

On June 22, 1998, FDA published nine interim final rules to prohibit use of a series of health claims about which notifications had been submitted to the Agency pursuant to FDAMA (FDA, 1998a, b, c, d, e, f, g, h, i). In one (FDA, 1998f), FDA concluded that the statement “Garlic is well known for its medicinal benefits: Lowering blood cholesterol, fighting off infections and boosting the immune system,” which was contained in a U.S. Department of Agriculture (USDA) press release, was not an authoritative statement for the purposes of FDAMA. FDA stated that USDA had advised FDA that the statement was “not an authoritative statement of USDA because it was not based upon a deliberative review of the scientific evidence”

exempted by FDA.²

NLEA also states that a health claim may be made only if the food “does not contain, as determined by [FDA] regulation, any nutrient in an amount which increases to persons in the general population the risk of a disease or health-related condition which is diet related, taking into account the significance of the food in the total daily diet” FDA has established these “disqualifying nutrient levels” as one of the general health claim requirements in 21 CFR § 101.14(a)(4), but may exempt certain foods.³ In addition, the health claim may not be false or misleading in any particular, which includes a prohibition on being misleading by failure to reveal facts that are material in the light of the claim.

Qualified Health Claims

FDA sets a rigorous standard of scientific evidence before it will issue a health claim regulation. However, more recently FDA announced it would also allow “qualified health claims.” In *Pearson v. Shalala* (164 F.3d 650 (D.C. Cir. 1999)), the U.S. Court of Appeals ruled that FDA must consider the possibility of approving health claims that incorporate qualified representations or “disclaimers.” An example might be “Preliminary research suggests that X nutrient reduces the risk of Y disease.”

In December 2002, FDA (FDA/CFSAN/ONPLDS, 2002) announced that it would indeed allow qualified health claims on conventional foods, as long as the claim was supported by the “weight of the evidence.” FDA also announced the Consumer Health Information for Better Nutrition Initiative and created a task force of representatives from FDA, the Federal Trade Commission and NIH (the FDA Task Force). The purpose of the FDA Task Force was to seek input from health professionals, industry, consumer groups, and academic and research organizations, and explore means of increasing the flow of science-based information to consumers regarding health benefits of conventional food and dietary supplements to encourage sound dietary decisions. A few weeks later, in *Whitaker v. Thompson* (248 F. Supp. 1 (D.D.C. 2002)), the U.S. District Court for the District of Columbia, interpreting the *Pearson* decision, found that FDA must apply a “credible evidence” standard rather than a “weight of the evidence” standard in evaluating qualified health claims.⁴

FDA subsequently acknowledged that the court decisions clarified the need to provide for health claims based on “somewhat settled science rather than just on the [SSA], as long as the claims do not mislead consumers” (FDA/CFSAN/ONPLDS, 2003b). In response to the court decisions and the FDA Task Force Report, FDA published

² Examples of foods exempted from the jelly bean rule are non-cariogenic chewing gums and candies, and salad dressings containing plant sterol/stanol esters (21 CFR §§ 101.80(c), 101.83(c)).

³ For example, for most foods these levels are 13.0 g total fat, 4.0 g saturated fat, 60 mg cholesterol, or 480 mg of sodium, per RACC, per labeled serving size, and, only for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g (21 CFR § 101.14(a)(4)). Among exempted foods are plant sterol/stanol containing spreads and salad dressings (21 CFR § 101.83(c)).

⁴ The Court concluded that the *Pearson* decision “implied, though it did not declare explicitly, that when ‘credible evidence’ supports a claim, that claim may not be absolutely prohibited.”

interim guidelines in July 2003 whereby qualified health claims can be made not only for dietary supplements but for conventional foods as well. The guidelines outline the petition procedure to be followed for qualified health claims (FDA/CFSAN, 2003a) and describe the evidence-based ranking system by which FDA will evaluate scientific data concerning such claims (FDA/CFSAN, 2003b).⁵

Under the interim procedures, if the Agency approves a qualified health claim petition, it will issue a letter to the petitioner (and publish a copy on its website) outlining the criteria the product must meet to bear the qualified health claim. This letter will indicate that the Agency will “exercise its enforcement discretion” to allow the claim. Thus, these claims will not become codified by regulation, although any product meeting the criteria, not just the petitioner’s, will still be allowed to use the claim.

The interim guidelines also describe a systematic evaluation of the strength of the scientific evidence concerning the qualified health claim. FDA’s evidence-ranking system is modeled after the system developed by the Institute for Clinical Systems Improvement as adapted by the American Dietetic Association. In evaluating the data, FDA will separately rate the design of each study, the quality of each study and the strength of the entire body of evidence, and, based on such ratings, assign a final rank to the scientific evidence in support of the qualified health claim. Different levels of scientific evidence will trigger different qualifying language. This scheme “grades” the evidence supporting the claim—with B, C or D levels identified as those for which the SSA standard cannot be met—and provides standardized qualifying language (see Table 5).

FDA began considering qualified health claims under the interim procedures on Sept. 1, 2003, and intends to continue to do so until regulations are promulgated by notice-and-comment rulemaking. In preparation for the rulemaking process, FDA published an advance notice of proposed rulemaking (ANPR) on Nov. 25, 2003 (FDA, 2003a) requesting comments on three regulatory alternatives for qualified health claims: (1) codify the interim guidelines on procedure and evidence-based ranking through notice-and-comment rulemaking, (2) apply the SSA standard to characterization of the scientific data rather than the substance-disease relationship and subject claims to notice-and-comment rulemaking, and (3) consider the claims outside NLEA and therefore subject only to the post-marketing ban against false or misleading claims, which

Table 5. Standardized Qualifying Language for Qualified Health Claims (FDA/CFSAN, 2003b)

Scientific Ranking ^a	FDA Category	Appropriate Qualifying Language ^b
Second Level	B	... “although there is scientific evidence supporting the claim, the evidence is not conclusive.”
Third Level	C	“Some scientific evidence suggests ... however, FDA has determined that this evidence is limited and not conclusive.”
Fourth Level	D	“Very limited and preliminary scientific research suggests ... FDA concludes that there is little scientific evidence supporting this claim.”

^a First level, FDA category A, refers to claims that meet the SSA standard.

^b The language reflects wording used in qualified health claims as to which the Agency has previously exercised enforcement discretion for certain dietary supplements. During this interim period, the precise language as to which the Agency considers exercising enforcement discretion may vary depending on the specific circumstances of each case.

includes claims lacking substantiation.

FDA stated that the first option “responds to the First Amendment concerns identified in *Pearson* by providing for the use of disclaimers to communicate to consumers the level of scientific evidence in support of health claims and to cure potentially misleading claims” (FDA, 2003a). Other advantages of the first option noted by the Agency are FDA pre-approval of claims, opportunity for public comment, faster review times (reviews would be completed in 270 days) and greater flexibility for revisions to claims as scientific data evolves.

FDA cited several drawbacks to the second option, including inflexibility, the burden of notice-and-comment rulemaking for each claim and vulnerability to First Amendment legal challenge due to lack of timeliness. Agency concerns about option three were identified as lack of FDA pre-approval, the burden of building enforcement cases (searching the literature, consulting experts and, in the case of possible implied claims, conducting consumer perception tests), and the absence of an opportunity for public comment.

A procedure patterned after the generally recognized as safe (GRAS) notification process, as recommended and discussed on page 45, would address the concerns articulated by FDA with respect to the three proposed options. A panel of independent experts, qualified by relevant training and experience, would evaluate the scientific evidence pertinent to a proposed qualified health claim and prepare a “generally recognized as efficacious” (GRAE) report that would be made publicly available. Companies wishing to use a qualified health claim would submit a notice to FDA containing the GRAE report and the proposed claim for review prior to use of the claim. Information concerning the training and experience of the qualified experts who prepared the GRAE report would also be made available to provide confidence in the scientific validity of the report. FDA would evaluate the submitted notice to determine whether there is sufficient basis for a GRAE determination for the proposed claim and respond by letter to the notifier. Public availability of the GRAE report, the claim notice and the FDA response letter would allow for input from consum-

⁵ On Aug. 6, 2004, the U.S. District Court for the District of Columbia dismissed a lawsuit filed by the Center for Science in the Public Interest and the Public Citizen Health Research Group, alleging that the FDA interim guidance would allow claims in violation of NLEA, on the basis of lack of ripeness and standing. *Center for Science in the Public Interest v. FDA*, Case No. 03-1962, filed Aug. 6, 2004.

ers and other interested parties. An established deadline for FDA's response would provide for timely reviews. As the scientific evidence evolved, notifiers could submit amended notices to FDA. The GRAE report would meet the need for a comprehensive expert review and evaluation of the scientific evidence for the claim, and the FDA notification process would allow for timely dissemination of the claim. The Agency would not face the burden of notice-and-comment rulemaking for each claim, and an FDA enforcement case could readily be made once the GRAE report and FDA's response to the claim notice established not only the generally recognized claim, but also its conditions and limitations.

In addition to the regulatory options for qualified health claims, the ANPR also requested comments on several issues identified in the FDA Task Force Report: (1) data and research on a substance-disease relationship, including incentives for developing the data needed to obtain significant scientific agreement, (2) revised claim language for qualified health claims, (3) use of interim final rules for health claims and the balance of timeliness versus comprehensiveness of FDA's review, (4) use of phrases such as "FDA authorized" in health claims, (5) consumer education, (6) data evaluations by outside scientific groups, (7) the definition of "competent and reliable scientific evidence" for purposes of supporting a qualified health claim, and (8) the definition and criteria for dietary guidance statements. The ANPR public comment period ended on Feb. 25, 2004. FDA also re-opened the comment period for a 1995 proposed rule on general requirements for health claims to seek comments on the minimum nutrient content and disqualifying nutrient levels requirements for health claims, and the use of abbreviated health claims. This new public comment period for the 1995 proposal ended on July 6, 2004 (FDA, 2004a).

To date, FDA has exercised enforcement discretion to allow qualified health claims for selenium and cancer, antioxidant vitamins and cancer, nuts and heart disease, walnuts and heart disease, omega-3 fatty acids and CHD, B vitamins and vascular disease, phosphatidylserine and cognitive dysfunction and dementia, folic acid and neural tube birth defects, and mono-unsaturated fats from olive oil and CHD. Most of these claims were considered by FDA as the health claims litigation evolved, although a few, including the omega-3 fatty acids and CHD claim and the olive oil and CHD claim for conventional foods, were evaluated after issuance of the interim guidelines. Several petitions for qualified health claims remain pending.

Nutrient Content Claims

A claim that expressly or implicitly characterizes the level of a nutrient (e.g., "high in vitamin C," "low in sodium") is known as a nutrient content claim. Such a claim generally may not be used in food labeling unless the claim is made in accordance with authorizing FDA regulations. (However, see the exceptional authorization for use of a nutrient content claim based on an authoritative statement

by a scientific body reviewed earlier in this section.)

FDA has authorized certain nutrient content claims for substances for which the Agency has established DRVs or RDIs. For example, generally, a food's labeling may claim that the food is "high in," "rich in," or an "excellent source of" a nutrient for which FDA has established an RDI if the food provides 20% or more of the RDI per RACC (21 CFR §101.54(b)). FDA has also published regulations authorizing (and establishing detailed requirements for) "good source," "more," and "light" (or "lite") claims, and certain claims about calorie content, sodium content, and fat, fatty acid, and cholesterol content in 21 CFR §§101.54-101.62. In addition, FDA recently requested data and information concerning a trans fatty acids nutrient content claim (FDA, 2003b, 2004b) and the use of synonyms not specifically listed in the nutrient content claims approving regulations (FDA, 2004a).

However, if a manufacturer wants to make a claim about a food being a good source of an additional nutrient for which no FDA nutrient content claim regulation already exists, the manufacturer may not be able to make the claim at all in labeling (even if the claim would be truthful and not misleading) unless and until FDA can be persuaded to issue an approving regulation to authorize use of the claim. For example, FDA has stated that "... a claim such as 'contains lycopene' would be an unauthorized nutrient content claim because lycopene does not have an RDI."

Nevertheless, FDA has also said that a labeling statement can be made to the effect that a food provides a stated amount of lycopene per serving, although any claim that suggests that the amount is substantial would not be permitted. For example, the Agency has said that a label statement such as "x mg of lycopene per serving" is permitted under 21 CFR §101.13(i)(3), which allows for the use of amount or percentage statements that do not implicitly characterize the level of the nutrient in a food (e.g., claims that do not imply whether the amount is high or low based on an established RDI or DRV value), so long as the statement is not misleading in any way (FDA, 1997a).

One may petition FDA to issue a regulation for a new nutrient content claim. The petition must show why use of the food component characterized by the proposed claim is of importance in human nutrition by virtue of its presence or absence at the levels that the claim would describe.

Note that, once issued, a new nutrient content claim regulation approves the use of a claim by any company whose product contains the referenced nutrient at the required level, i.e., such a regulation is not an exclusive license that applies only to the person who has petitioned for the issuance of the regulation.

As in the case of health claims, FDAMA also amended the FDC Act to authorize the use in labeling of certain nutrient content claims that are the subject of a published authoritative statement by a scientific body of the U.S. Government or NAS. Such a nutrient content claim must use a term (e.g., "high" in, "good source" of) that is already defined by FDA in its regulations. The choline nutrient

content claim is the only notified nutrient content claim allowed thus far (FDA/CFSAN/ONPLDS, 2001). The choline claim is based on the same NAS report as the existing notified health claims discussed above.

If a food is specially formulated for the feeding of a patient who has “special medically determined nutrient requirements,” and the food is labeled to be used under the supervision of a physician (or under medical supervision), the food’s labeling may bear information about its usefulness for the dietary management of a disease or medical condition “for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.” Such foods are known as “medical foods” (21 CFR §101.9(j)(8)).

If a food qualifies as a medical food, it is exempt from the requirements that otherwise apply for approval of health claims and nutrient content claims used in labeling (21 CFR §101.14(f)(2))⁶. A company that is responsible for a medical food must possess data that are sufficient to show that no claim made on the label or in other labeling is either false or misleading, but there is no requirement to obtain FDA approval or even to notify FDA that one is manufacturing or marketing a medical food.

Note that a medical food is not authorized to bear a claim to cure, mitigate, treat, or prevent a disease; as discussed above, such a claim would create drug status for the product. Instead, a medical food is permitted to make a claim to address a patient’s special dietary needs that exist because of a disease or medical condition; this type of claim is distinguished from a claim to treat the disease. As an example, the following claim would be appropriate for a medical food: “For use under medical supervision, this product can be helpful in the dietary management of X disease or medical condition.”

At first impression, the medical food provision may appear to be outside the scope of interest for a company that wants to sell conventional foods. However, it should be recognized that the number of consumers who are “patients” and for whom particular types of medical foods might be of interest is substantial and growing. Medical food status also can be an initial “bridge” mechanism for introducing a product that is subsequently promoted to a wider segment of the population. Ensure[®] appears to have gained its foothold in the marketplace in this manner.

Statements of Nutritional Support for Dietary Supplements

The Dietary Supplement Health and Education Act (DSHEA) defines dietary supplements as food products that (a) are intended to be ingested in the form of a tablet, capsule, powder, soft gel, gel cap, or liquid droplet (or, if not intended for ingestion in such a form, that are not represented to be useful either as a conventional food or as a sole item of a meal or the diet) and (b) provide a vitamin,

mineral, herb or other botanical, amino acid, or other “dietary substance” (including a concentrate, metabolite, constituent, extract, or combination of any of the above) (21 USC § 321(ff)).

As described above, it generally is not permitted to make a health claim in labeling for a food (including a dietary supplement) unless the claim meets the FDA approval or FDAMA authoritative statement requirements for health claims. However, for dietary supplement products only, there is an exception to the usual requirements for use of health claims that permits four types of “statements of nutritional support” to be made in labeling without complying with the usual requirements for health claims. These exceptional statements of nutritional support are as follows:

- a statement that “claims a benefit related to a classical nutrient deficiency disease and discloses the prevalence of such disease in the United States;”
- a statement that “describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans;”
- a statement that “characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function;” and
- a statement that “describes general well being from consumption of a nutrient or dietary ingredient” (21 USC § 343(r)(6)).

Any of the above four types of statements of nutritional support may be made in labeling for a dietary supplement, without the approval of a health claim regulation, if:

- the manufacturer has substantiation that such statement is truthful and not misleading;
- the labeling contains, prominently displayed, the following additional text, “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease;” and
- the manufacturer notifies FDA no later than 30 days after the first marketing of the dietary supplement with the statement (21 USC §343(r)(6)).

After this legislation (part of DSHEA) was passed in 1994, it appeared at first that there might be reluctance within the dietary supplement industry to use the statement of nutritional support exemption from health claim clearance requirements because of the mandated “disclaimer” labeling. However, thousands of statements of nutritional support have now been filed with FDA by companies that have told the Agency that they are using the statements in labeling.

FDA recently published a draft guidance describing the amount, type and quality of scientific evidence that the Agency recommends a manufacturer possess to substantiate a statement of nutritional support made for a dietary supplement (FDA/CFSAN/ONPLDS, 2004c). While the guidance does not constitute legally enforceable criteria, it does provide useful insight into FDA’s current view of the “competent and reliable scientific evidence” standard that FDA will apply in

⁶ On Nov. 29, 1996, FDA published an ANPR (FDA, 1996a) “to initiate a reevaluation of ... the regulation of ... medical foods,” but then withdrew the ANPR on Nov. 26, 2004 (FDA, 2004c).

evaluating support for such a claim. FDA's guidance recommends that manufacturers consider four factors in assessing substantiation for a claim: the meaning of the claim, the relationship of the evidence to the claim, the quality of the scientific evidence and the totality of the scientific evidence.

On Jan. 6, 2000 (FDA, 2000a), FDA published final regulations that specify whether particular types of claims will be deemed by the Agency to be unacceptable disease claims (i.e., not to be acceptable structure/function claims) in the labeling of dietary supplements (21 CFR § 101.93(f), (g)). Key provisions of these regulations are described below.

Definition of Disease

The definition of "disease or health-related condition" mirrors that in the health claims rule in 21 CFR § 101.14(a)(5). Thus, a "disease" is "damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition" (21 CFR §101.93(g)(1)).

Claims Relating to Signs or Symptoms of Disease

The regulations provide that a labeling statement will be deemed to be a prohibited disease claim if the statement claims, explicitly or implicitly, that the product has an effect on a specific disease or class of diseases, or "on the characteristic signs or symptoms of a specific disease or class of diseases, using scientific or lay terminology" (21 CFR §101.93(g)(2)(i)-(ii)).

Fig. 4 provides some of the examples of permissible structure/function claims and impermissible disease claims provided by FDA in the preamble to the final regulations (FDA, 2000a).

FDA states that some minor pain relief claims may be appropriate structure/function claims for dietary supplements, since minor pain is not always associated with a disease. To illustrate, FDA states that an acceptable dietary supplement claim would be to relieve "muscle pain following exercise," whereas a claim to relieve "joint pain" would not be acceptable because joint pain is a characteristic symptom of arthritis. In addition, FDA states that the Agency does not believe the law authorizes a product whose name promises pain relief ("pain-free" or "pain product") and whose labeling includes claims related to maintenance or support of joints.

Claims Concerning Conditions Associated with Natural States

FDA states that "mild conditions commonly associated with particular stages of life or normal physiological processes" will not be considered diseases under the final regulations (FDA, 2000a). FDA provides the following as examples of conditions "about which structure/function claims could be made:"

- (1) Morning sickness associated with pregnancy;⁷
- (2) leg edema associated with pregnancy;
- (3) mild mood changes, cramps, and edema associated with the menstrual cycle;
- (4) hot flashes;
- (5) wrinkles;
- (6) other signs of aging on the skin, e.g., liver spots, spider veins;
- (7) presbyopia (inability to change focus from near to far and vice versa) associated with aging;
- (8) mild memory problems associated with aging;
- (9) hair loss associated with aging; and
- (10) noncystic acne.

FDA states, however, that claims to relieve conditions such as the following would be disease claims under the final regulations: toxemia of pregnancy; osteoporosis; glaucoma; arteriosclerotic diseases of coronary, cerebral or peripheral blood vessels; cystic acne; severe depression associated with the menstrual cycle; and benign prostatic hypertrophy. FDA also states that the claim "helps to maintain normal urine flow in men over 50" is a disease claim.

Structure/Function Claims Included in the OTC Drug Review

Under the final regulations, certain claims that are included in the FDA's OTC (Over-The-Counter) Drug Review may nevertheless be acceptable structure/function claims for the labeling of a dietary supplement, although other claims from the OTC Drug Review would be deemed by FDA to remain exclusively disease claims that are not acceptable for dietary supplements. For example, FDA states that claims that are included in the "antacid" OTC drug monograph but that also may be acceptable structure/function claims include "relief of sour stomach" and "relief of upset stomach," because the claims refer to a nonspecific group of conditions that have a variety of causes, many of which are not disease-related. However, claims relating to the relief of "heartburn" or "acid indigestion," without further qualification, are said by FDA not to be appropriate structure/function claims. On the other hand, claims related to "occasional heartburn" or relief of "occasional indigestion" are said to be potentially appropriate structure/function claims.

A claim from the antiemetics OTC drug monograph—"for the prevention and treatment of the nausea, vomiting, or dizziness associated with motion"—is now said by FDA to be a permitted structure/function claim.

Certain "laxative" and "weight loss" claims are also permissible as structure/function claims under the final regulations. FDA states that use of the term "laxative" is not a disease claim provided that the labeling makes clear that the product is intended for use "in the treatment of occasional rather than chronic constipation."

Generally, weight loss claims may be considered appropriate structure/function claims, provided that the labeling does not suggest an effect on obesity. A permissible structure/function claim may be made to "suppress appetite."

⁷ On Feb. 9, 2000, FDA issued a "Statement Concerning Structure/Function Rule and Pregnancy Claims" (HHS/FDA, 2000). FDA stated that, to ensure that careful consideration is given to concerns recently raised regarding how the structure/function rule relates to pregnancy, FDA today is advising dietary supplement manufacturers not to make any claims related to pregnancy on their products based on the Agency's recently issued structure/function rule.

Fig. 4. Examples of Permissible Structure/Function Claims

Permissible “Structure/Function Claims”	Impermissible “Disease Claims”
Helps to maintain cholesterol levels that are already within the normal range ^a	Lowers cholesterol
Helps support cartilage and joint function	Inhibits platelet aggregation ^b
Maintains healthy lung function	Prevents bone fragility in post-menopausal women
Improves absentmindedness	Maintains normal bone density in post-menopausal women
Relieves stress and frustration	Maintains healthy lungs in smokers
	Prevents irregular heartbeat
	Relieves alcohol intoxication
	Use as part of your diet when taking insulin to help maintain a healthy blood sugar level
	Promotes general well being during the cold and flu season, and dietary support during the cold and flu season

^a FDA also states that references to “healthy” cholesterol “may be misleading to consumers,” since the phrase is now frequently used to refer to high density lipoproteins (FDA, 2000a).

^b In the proposed rule, FDA had indicated that this claim would not be considered an implied disease claim.

FDA also states that “helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness” would be a permissible stimulant-type structure/function claim, provided that the product’s labeling would not imply treatment of chronic fatigue syndrome or narcolepsy.

Citations to Publications that Refer to Disease

Under the final regulations, the use in dietary supplement labeling of a citation to a scientific publication that mentions disease will be considered a disease claim “if, in the context of the labeling as a whole, the citation implies treatment or prevention of a disease” (21 CFR § 101.93(g)(2)(iv)(C)). In evaluating the use of such citations, FDA states that it will consider both the “prominence” of the citations and whether a cited article provides “legitimate support” for a proper structure/function claim that appears in the labeling. On the other hand, FDA states that including a citation to a scientific reference that mentions a disease on the immediate product label or packaging will be considered a disease claim.

The Jan. 6, 2000, final rule (FDA, 2000a) includes a significant change in the Agency’s overall regulatory views about dietary supplement labeling: FDA now asserts that all structure/function claims that are made on the label or in other labeling for dietary supplement products must be submitted to FDA within 30 days after the claim is first used, and must use the so-called “DSHEA disclaimer” (i.e., “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease”).

Formerly, FDA had accepted that a structure/function claim did not need to meet these two provisions if the structure/function claim derived from “nutritional value” or from “nutritive value.” However, the final rule recanted this more permissive interpretation (from Sept. 23, 1997 (FDA, 1997b)). The new interpretation subjects a structure/function

claim used in labeling for a dietary supplement to requirements that do not apply if the same claim is used in labeling for a conventional food. For example, a dietary supplement manufacturer making the claim “calcium helps build strong bones” would need to notify FDA and to use the DSHEA disclaimer. In contrast, a company that manufactures a conventional food that is a good source of calcium could make the same claim on the label for that food without any need to notify FDA or to include any disclaimer language in its labeling.

It is important to note that many companies within the dietary supplement industry maintain that FDA’s new interpretation is in error as a matter of law and are continuing to follow FDA’s former interpretation. This has led to considerable inconsistency and confusion in the marketplace. Several dietary supplement trade associations and at least one company filed formal petitions with FDA for reconsideration and stay of the Agency’s new interpretation. FDA invited comments on these petitions, and the matter remains pending at this time (2000b).

Structure/Function Claims for Conventional Foods

As described above, the FDC Act provides that products that are “intended to affect the structure or any function of the body” generally are subject to regulation as drugs, but this does not apply in the case of food. Accordingly, it has long been recognized that a food may make labeling representations about its dietary impact on the structure or function of the human body, provided that the particular claim used does not also represent that the food will cure, mitigate, treat, or prevent disease (which would create drug status), and provided further that the claim does not trigger some other requirement for FDA preclearance (e.g., if a particular claim about impact on structure or function is a claim that also would be regarded as a health claim, the claim would need to comply with health claim requirements, as described above).

In practice, companies have made a few claims of this type that FDA generally has accepted over the years, without asserting that the claim creates drug status or that the claim is a health claim that requires compliance with health claim requirements. For example, claims of the general type “calcium helps build strong bones” or “protein helps build strong muscles” have long been made in food labeling and appear generally to have been accepted by FDA as appropriate claims about the impact of a food on the structure or function of the body.

In principle, it would appear that this type of claim could be extended (assuming that a company possesses substantiating data that show that the claim is truthful and not misleading, of course). For example, it would appear to be proper to make a truthful and nonmisleading claim to the effect that a substance in a food “helps maintain a normal,

healthy cardiovascular system” without triggering either drug status or requirements for approval of a health claim.⁸ However, there is considerable uncertainty about how far this type of structure/function claim can be “pushed” before FDA will assert either drug status or health claim status.

In a preamble in the *Federal Register* of Sept. 23, 1997 (FDA, 1997b), FDA stated as follows:

FDA points out that the claim that cranberry juice cocktail prevents the recurrence of urinary tract infections ... is a claim that brings the product within the “drug” definition ... because it is a claim that the product will prevent disease. However, a claim that cranberry products help to maintain urinary tract health may be permissible on ... cranberry products in conventional food form ... if it is truthful, not misleading, and derives from the nutritional value of cranberries. If the claim derives from the nutritive value of cranberries, the claim would describe an effect of a food on the structure or function of the body and thus fall under one exception to the definition for the term “drug”... . The claim is not a health claim because no disease is mentioned explicitly or implicitly... .

Clearly, there is considerable opportunity to make labeling claims about the favorable impact of a food on the normal, healthy structure or function of the human body.

However, some have maintained that FDA’s insistence on derivation from “nutritional” or “nutritive” value is not a correct statement of the law. As defined by the FDC Act, the term “drug” means “... articles (other than food) intended to affect the structure or any function of the body of man,” and “food” includes “(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article” (21 USC §§ 321(g)(1)(C), (f)).

In reviewing the definition, the U.S. Court of Appeals for the Seventh Circuit stated:

When the statute defines “food” as “articles used for food,” it means that the statutory definition of “food” includes articles used by people in the ordinary way most people use food—primarily for taste, aroma, or nutritive value. To hold ... that articles used as food are articles used solely for taste, aroma or nutritive value is unduly restrictive since some products such as coffee or prune juice are undoubtedly food but may be consumed on occasion for reasons other than taste, aroma, or nutritive value (*Nutrilabs v. Schweiker*, 713 F.2d 335, 338 (7th Cir. 1983)).

This interpretation has been accepted by other federal

courts (*American Health Products Co. v. Hayes*, 574 F. Supp. 1498 (S.D.N.Y. 1983), *aff’d*, 744 F.2d 912 (2d Cir. 1984)).

Thus, the courts have recognized that the food exemption from the drug definition in the FDC Act is not limited to nutritional or nutritive substances. According to established case law, an article may be a food within the meaning of the FDC Act if it is used “primarily” for taste, or for aroma, or for nutritional value; in addition, sometimes a food—such as coffee or prune juice—will not even be used for any of these three purposes. The exclusion from “drug” status for a “food” in the FDC Act is therefore not properly limited only to products that are “nutritional” or “nutritive”—because “food” is much broader than that.

Since a food’s effects need not be of a nutritional nature, there is no apparent reason why a food may not properly provide labeling information about its effects on the structure or function of the body that do not derive from nutritional value. Indeed, in *American Health Products v. Hayes*, the U.S. District Court for the Southern District of New York stated plainly:

... if an article affects bodily structure or function by way of its consumption as a food, the parenthetical [i.e., the “(other than food)” provision in 21 USC § 321(g)(1)(C)] precludes its regulation as a drug notwithstanding a manufacturer’s representations as to physiological effect The presence of the parenthetical in [21 USC § 321(g)(1)(C)] suggests that Congress did not want to inhibit the dissemination of useful information concerning a food’s physiological properties by subjecting foods to drug regulation on the basis of representations in this regard (*American Health Products Co. v. Hayes*, 574 F. Supp. 1498, 1507 (S.D.N.Y. 1983)).

Thus, the courts have recognized that coffee may be used to help stay alert, or that prune juice may be used to help promote regularity, and that labeling claims about this type of physiological effect are appropriate for a food and do not create drug status—regardless of whether such effects and claims derive from the nutritional/nutritive value of the food. Even if it were true that a structure/function claim for a food should derive from nutritional value, the Agency’s statements about the meaning of the term have been inconsistent. In the same 1997 *Federal Register* document (FDA, 1997b), FDA stated that even though the term “statement of nutritional support” was used by Congress, FDA chose not to use the term in the regulations “because many of the substances that can be the subject of this type of claim do not have nutritional value. Thus, the term ‘statement of nutritional support’ is not accurate in all instances.” One could argue that the FDA objection is in conflict with the express intention of Congress to give a broad meaning to “nutritional,” and therefore contrary to law. Nevertheless, this FDA statement certainly suggests an FDA view that nutritional is a concept that should be interpreted critically and narrowly.

However, in the context of defining the scope of a

⁸ In two letters to manufacturers of margarine-type products, the Agency advised that claims of this type may appropriately be made as structure/function claims. In letters to Lipton (FDA, 1999a) and McNeil Healthcare (FDA, 1999b), FDA agreed that vegetable oil sterol esters and plant stanol esters, respectively, are GRAS for use in vegetable oil spreads “to supplement the nutritive value of the spread, and to help structure the fat phase and reduce the fat and water content of the spread.” FDA also stated that the Agency regarded the claim, “Helps promote healthy cholesterol levels as part of a diet low in saturated fat and cholesterol” as a proper structure/function claim.

nutrient content claim, FDA proceeded in the opposite direction and asserted that the term “nutrient” is not narrow at all, but instead very broad and includes many substances that traditional nutritionists might not regard as nutritional. In this context, FDA stated that “nutrient” encompasses a long list of examples included in a discussion between Senators Metzenbaum and Symms before passage of NLEA in 1990. The quoted list of agreed-upon examples of nutritional substances includes:

Primrose oil, black currant seed oil, cold pressed flax seed oil, “Barleygreen” and similar nutritional powdered drink mixes, Coenzyme Q10, enzymes such as bromelain and quercetin, amino acids, pollens, propolis, royal jelly, garlic, orotates, calcium-EAP (colamine phosphate), glandulars, hydrogen peroxide (H₂O₂), nutritional antioxidants such as superoxide dismutase (SOD), and herbal tinctures (FDA, 1997b).

Moreover, both of these discussions fail to reference the Agency’s own definition of nutritive value: “a value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients that cannot be produced in sufficient quantities by the body, or providing energy.”⁹

Considering the Congressional intent and some of the Agency’s own statements, it would appear that even if FDA were correct in tying structure/function claims to nutritional value, the meaning of nutritional in this context would need to be regarded very broadly. As stated in the summary report of a public meeting on the conceptual framework for structure/function claims for conventional foods posted on FDA’s website, “Nutritive value cannot be defined simply in terms of source, dose or biochemical composition.” (FDA/CFSAN/ONPLDS, 2000b)

⁹ 21 CFR § 101.14(a)(3). It is instructive to note that when FDA published this regulation, (FDA, 1993a), the Agency included the following explanatory discussion:

FDA recognizes that certain substances can play a major role in reducing the risk of certain chronic diseases and may confer their benefits through a number of processes. Accordingly, the Agency has worded the definition of “nutritive value” in new § 101.14(a)(3) to provide significant flexibility in determining whether a substance possesses such value. FDA used the phrase “such . . . as” in the definition to ensure that the three referenced processes will be understood to be general examples of the ways in which a substance may legitimately confer nutritive value, rather than as an all-inclusive list.

The Agency believes that it is inappropriate to codify findings of nutritive value for specific substances. Such findings would only serve to undermine the intended flexibility of the definition because an extended listing of those substances that possess nutritive value could be interpreted as an exclusive list (FDA, 1993a).

Claims About Special Dietary Uses

Since 1938 the FDC Act has recognized that it is proper for a food to be labeled with claims “for special dietary uses.” FDA is given authority to issue regulations that require additional informative labeling for foods that are represented for special dietary uses.

In the past, FDA issued regulations requiring certain additional labeling information for certain types of foods for special dietary uses (21 CFR Part 105). There continues to be a regulation of this type that governs the use of “hypoallergenic” labeling (21 CFR § 105.62). This regulation provides that if a food is represented “for special dietary use by reason of the decrease or absence of any allergenic property or by reason of being offered as food suitable as a substitute for another food having an allergenic property,” the label of the food must bear certain information, including the “quantity or proportion of each ingredient (including spices, flavoring, and coloring).”

FDA has said that if a claim that otherwise would require FDA approval as a health claim is already authorized by a regulation concerning special dietary use, FDA will not require that a new health claim regulation also be issued. Accordingly, if a company is interested in using a new labeling claim that would fall within the definition of a health claim, then instead of petitioning FDA to issue an approving health claim regulation, the company may be able to petition the Agency to issue a special dietary use labeling regulation. However, this is a largely theoretical option. In practice, FDA has avoided issuing new special dietary use regulations in recent years; indeed, the Agency has been revoking some of these regulations.

General Freedom to Use Statements That Are Not ‘False Or Misleading In Any Particular’

In addition to the various authorizations to use particular types of health-related claims as discussed above, it should also be remembered that the FDC Act contains no general requirement that statements included in labeling of FDA-regulated foods must be approved by FDA prior to use. Instead, requirements for FDA preclearance are confined to certain specific types of labeling statements (e.g., health claims), and except for such specific requirements, food labeling generally may include any statement, so long as it is truthful and not misleading in any particular.

Scientific Standards for Evaluating a Proposed Claim

The evidence supporting a functional food claim must meet certain standards. The level of support for these claims ranges from significant scientific agreement (SSA) for approved health claims to “FDA has determined that this evidence is limited and not conclusive” and two other qualifying levels of data within this range for qualified health claims (FDA/CFSAN, 2003a) to “competent and reliable scientific evidence” for structure/function claims (FDA/CFSAN/ONPLDS, 2004c). The application of any standard is intended to be objective and based on a body of sound and relevant scientific data. It is also intended to be flexible, recognizing the variability in the amount and type of data needed to support the validity of different substance/health relationships.

Significant Scientific Agreement

When FDA evaluates a petition for approval of a health claim, it issues a regulation only when it determines that there is “significant scientific agreement” that the claim is supported by scientific evidence. This evaluation considers whether experts (qualified by scientific training and experience to evaluate such claims) would agree that the claim is valid based on the totality of publicly available scientific evidence (including evidence from well designed studies conducted in a manner consistent with generally recognized scientific procedures and principles).

In explaining its SSA standard for health claims, FDA stated:

The standard of scientific validity for a health claim includes two components: (1) that the totality of the publicly available evidence supports the substance/disease relationship that is the subject of the claim, and (2) that there is SSA among qualified experts that the relationship is valid (FDA/CFSAN/OSN, 1999).

FDA further described SSA:

FDA’s determination of when SSA has been achieved represents the Agency’s best judgment as to whether qualified experts would likely agree that the scientific evidence supports the substance/disease relationship that is the subject of a proposed health claim. The SSA standard is intended to be a strong standard that provides a high level of confidence in the

validity of a substance/disease relationship. SSA means that the validity of the relationship is not likely to be reversed by new and evolving science, although the exact nature of the relationship may need to be refined. Application of the SSA standard is intended to be objective, in relying upon a body of sound and relevant scientific data; flexible, in recognizing the variability in the amount and type of data needed to support the validity of different substance/disease relationships; and responsive, in recognizing the need to re-evaluate data over time as research questions and experimental approaches are refined. SSA does not require a consensus or agreement based on unanimous and incontrovertible scientific opinion. However, on the continuum of scientific discovery that extends from emerging evidence to consensus, it represents an area on the continuum that lies closer to the latter than to the former (FDA/CFSAN/OSN, 1999).

FDA has specifically mentioned that SSA is not consensus:

Although SSA is not consensus in the sense of unanimity, it represents considerably more than an initial body of emerging evidence. Because each situation may differ with the nature of the claimed substance/disease relationship, it is necessary to consider both the extent of agreement and the nature of the disagreement on a case-by-case basis. If scientific agreement were to be assessed under arbitrary quantitative or rigidly defined criteria, the resulting inflexibility could cause some valid claims to be disallowed where the disagreement, while present, is not persuasive (FDA/CFSAN/OSN, 1999).

In assessing the validity of codified health claims, FDA has considered three types of evidence (Keystone Center, 1996):

- Epidemiology: data derived from observational studies assessing associations between food substances and disease;
- Biological mechanisms: data derived from chemical, cellular, or animal models investigating plausible mechanisms of action for food substances;
- Intervention trials: controlled assessment of clinical food substance interventions in the human population. The “gold standard” is the randomized controlled clinical trial.

FDA felt that these combinations of data met the SSA standard of proof (FDA/CFSAN/OSN, 1999). A number of sequential threshold questions are addressed in the review of the scientific evidence:

- Have studies appropriately specified and measured the substance that is the subject of the claim?

- Have studies appropriately specified and measured the disease that is subject of the claim?
- Are all conclusions about the relationship between the substance and the disease based on the totality of the publicly available scientific evidence?

The assessment of SSA then derives from the conclusion that a sufficient body of sound, relevant scientific evidence shows consistency across different studies and among different researchers and permits the key determination of whether a change in the dietary intake of the substances will result in a change in a disease or structure/function endpoint.

Weight of the Scientific Evidence

In its December 2002 announcement regarding qualified health claims, FDA indicated that codified health claims would still require substantiation meeting the SSA standard. In its initial guidance on qualified health claims, the Agency said it would use a “weight of the scientific evidence” (WOSE) standard to establish qualified health claims (FDA/CFSAN/ONPLDS, 2002). At that time, the following was proposed:

To meet the criteria for a qualified health claim, the petitioner would need to provide a credible body of scientific data supporting the claim. Although this body of data need not rise to the level of SSA defined in FDA’s previous guidance, the petitioner would need to demonstrate, based on a fair review by scientific experts of the totality of information available, that the “weight of the scientific evidence” supports the proposed claim. The test is not whether the claim is supported numerically (i.e., whether more studies support the proposed claim than not), but rather whether the pertinent data and information presented in those studies is sufficiently scientifically persuasive. For a claim that meets the WOSE standard, the Agency would decline to initiate regulatory action, provided the claim is qualified by appropriate language so consumers are not misled as to the degree of scientific uncertainty that would still exist.

FDA anticipates that this policy will facilitate the provision to consumers of additional, scientifically supported health information. FDA expects that, as scientific inquiry into the role of dietary factors in health proceeds, particular qualified health claims will be further substantiated, while for other qualified health claims the “weight of the scientific evidence” will shift from “more for” to “more against.” It is conceivable, therefore, that the information provided to consumers through qualified health claims in food labeling could change over time. FDA nevertheless believes that the dissemination of current scientific information concerning the health benefits of conventional foods and dietary supplements should be encour-

aged, to enable consumers to make informed dietary choices yielding potentially significant health benefits.

In July 2003, FDA published *Guidance for Industry and FDA for Interim Evidence-based Ranking System for Scientific Data* (FDA/CFSAN, 2003b). As stated in this document, “FDA has tentatively chosen to model its evidence-based rating system on that of the Institute for Clinical Systems Improvement as adapted by the American Dietetic Association (ADA) with modifications specific to FDA. In making this tentative decision, FDA relied on criteria for evaluating evidence-based rating systems as reviewed and critiqued by the Agency for Healthcare Research and Quality. FDA also found the modifications from ADA to be particularly useful as they considered diet and health relationships, whereas other groups focused on drug and treatment applications.” The elements of the evidence-based rating system include:

- Define the substance/disease relationship;
- Collect and submit all relevant studies;
- Classify, and therefore rate, each study as to type of study;
- Rate each study for quality;
- Rate the strength of the total body of evidence; and
- Report the “rank.”

The criteria used to determine the ranking of scientific evidence would include: satisfying the necessary quality level for studies, meeting prescribed design types, considering the number of individuals tested, and confirming that study results are relevant to the target population. When rating the strength of the total body of evidence, “the rating system is based on three factors: quantity, consistency, and relevance to disease risk reduction in the general population or target subgroup.” The first level of ranking meets the SSA standard and reflects “a high level of comfort” that the claimed substance/disease relationship is scientifically valid. The second level is the highest level for a qualified health claim and represents “a moderate/good level of comfort” that the claimed relationship is scientifically valid. Qualified experts would rank the relationship as “promising,” but not definitive. The third level represents “a low level of comfort” that the claimed relationship is scientifically valid. The fourth level is the lowest level for a qualified health claim and represents “an extremely low level of comfort” that the claimed relationship is scientifically valid. “If the scientific evidence to support the substance/disease relationship is below that described as the fourth level, no claim will be appropriate,” FDA stated.

Shortly after publication of FDA’s guidance on WOSE, the U.S. District Court for the District of Columbia ruled in *Whitaker v. Thompson* that “credible evidence” rather than “weight of the evidence” is the appropriate standard for FDA to apply in evaluating qualified health claims.¹⁰ Thus, FDA’s evaluation of WOSE will be tempered by the test of

¹⁰248 F. Supp. 2d at 12. The Court stated that the complete ban of a claim would be approved “only under narrow circumstances—where there was little-to-no scientific evidence in support of the claim and where [FDA] could prove that the public would still be deceived by the claim even with the use of accompanying disclaimers.”

“credible evidence” (FDA, 2003a).

The IFT Expert Panel believes the guidance can serve as a useful tool and assist in evaluating data. However, in the final analysis, most decisions will be based more on subjective judgment than on quantitative analysis. Therefore, a WOSE standard, tempered by the test of “credible evidence,” should be the basis for qualified health claims.

Competent and Reliable Scientific Evidence

In November 2004, FDA provided guidance to industry for determining whether the available information consti-

tutes “competent and reliable scientific evidence” for structure/function claims for dietary supplements, including:

- Does each study or piece of evidence bear a relationship to the specific claim(s)?
- What are the individual study’s or evidence’s strengths and weaknesses?
- If multiple studies exist, do the studies that have the most reliable methodologies suggest a particular outcome?
- If multiple studies exist, what do most studies suggest or find/does the totality of the evidence agree with the claim(s)? (FDA/CFSAN/ONPLDS, 2004c).

Limitations of Current Policies

The best regulatory policies are grounded in sound science and modified periodically as new knowledge becomes available. The current legal and regulatory structure for food has served our society well in many ways, but, like any patchwork system created over decades, it has areas where the existing requirements are no longer in keeping with today's needs. Certain current policies limit the scope and accuracy of consumer information about functional foods; other policies hinder the development and marketing of innovative functional foods, denying those health benefits to consumers. In deliberating and reviewing the science related to functional foods, the IFT Expert Panel identified the policy limitations below and formulated science-based recommendations that would enhance the development and marketing of functional foods.

Wording Claims to Avoid Drug Classification

To avoid drug classification, some claims may not accurately convey the actual effects of the food and may confuse consumers. Sometimes compliance with the regulations results in misleading (if not outright false) statements of the underlying science.

Currently, the wording of structure/function claims and health claims cannot imply a disease claim. The words used to describe health claims must be carefully phrased so that the claim is true and not misleading and so that it is in compliance with the requirements of current food and drug regulations.

The FDA rule regarding structure/function claims (FDA, 2000a) lists criteria and examples of proper structure/function claims compared to disease (drug) claims. Phrasing structure/function claims to avoid implying that the food prevents a certain disease often results in convoluted claims that contradict the supporting science.

For example, a claim that a food lowers cholesterol would be considered a drug claim because it implies abnormal cholesterol levels. Thus, functional foods that affect cholesterol levels state that the food “maintains normal cholesterol levels,” which is a permissible structure/function claim. However, such a statement is potentially misleading if the food in fact lowers cholesterol levels.

This issue is not merely academic, as products currently on the market demonstrate. Because of the stature given structure/function claims for dietary supplements at the time

when spreads containing stanol/sterol esters were to come on the market, a decision was made by the manufacturers to offer the spreads as a dietary supplement with a structure/function claim. FDA would not accept this classification, informing the manufacturers that the spreads containing these ingredients were in fact foods. Generally recognized as safe (GRAS) status was then established for the stanol/sterol esters. This was during a time when the future policies for structure/function claims for food remained unclear. Therefore, a petition for a health claim was filed linking consumption of phytosterol and phytosterol esters to a reduced risk of heart disease. After the time-consuming and costly health claim petition was approved, then the related cholesterol-lowering “disease” claim was allowed on the label.

The IFT Expert Panel recommends that product labeling be allowed to accurately reflect the scientific evidence. As long as claims are scientifically valid, enormous public health benefits would result from having consumers understand and act on the claimed product benefit. The Expert Panel anticipates very few potential problems from structure/function claims that imply reduction of disease risk (e.g., “lowers cholesterol” equals lower risk of heart disease) if the claims have adequate scientific basis. The potential benefit may improve the public health (e.g., lowering serum cholesterol from increased consumption of the food or low fat diet).

Defining Nutritive Value

Current FDA policy requires that the health benefit attributed to a food component be derived from its “nutritive value.” FDA states that, “nutritive value means a value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy” (21 CFR §101.14(a)(3)). There is no consensus on the meaning of this definition, and conflicts exist between legislation, regulations, and other Agency documents. Tying health benefits to nutritive value has proven to be a very restrictive policy from the standpoint of recognizing the advances of nutrition science and communicating beneficial information about foods to consumers.

The IFT Expert Panel recommends that FDA not restrict the health effects of foods to the very limited concept of nutritive value. Rather, the Expert Panel supports basing structure/function and health claims on a broad-based scientific criterion that addresses the extensive links between health and nutrition and other scientific disciplines such as physiology, endocrinology, biochemistry, neurology, and genetics. This interpretation is consistent with the desires of all parties. Consumers, manufacturers, and regulators want the same thing: credibility in the claims on food products. Credibility clearly depends on good science, and, to date, when the

science has been good, FDA has found a way to approve new ingredients and new claims. Therefore, the Expert Panel believes that regulatory oversight will be more consistent and appropriate if FDA replaces “nutritive value” with a more appropriate definition: “that benefits for functional foods should be based on nutritive value or through the provision of a physical or physiological effect that has been scientifically documented or for which a substantial body of evidence exists for plausibility.”

The two case studies presented below demonstrate where confusion pertaining to nutritive value was a major impediment to providing appropriate health information and/or new products to consumers.

Case Study: Stanol and Sterol Esters and Coronary Heart Disease

An example of the problems presented by requiring demonstration of “nutritive value” may be further understood by reviewing the case of stanol esters and sterol esters used in BENECOL® and Take Control® spreads, respectively. FDA has stated that a structure/function claim made for a conventional food product (but not for a dietary supplement) must be based on “nutritive value” because foods are legally defined as consumed primarily for “taste, aroma, or nutritive value.”

The first of the two spread products to be marketed was BENECOL. Prior to going to market, the manufacturer shared its planned labels with FDA, and it was apparent that the product would be marketed as a dietary supplement. Under that planned positioning, the “nutritive value” issue would have been irrelevant. However, FDA rejected its sale as a supplement, arguing that it resembled, and would be used as, a conventional food. In repositioning BENECOL as a food, the issue of “nutritive value” became germane, as it did for Take Control, because their stanol and sterol ester ingredients, respectively, were the basis of their cholesterol structure/function claims.

Ultimately, FDA allowed both products to be marketed as conventional foods. The basis for the Agency’s conclusion that the ingredients provided “nutritive value” is that any substance added to foods also must have either taste, aroma, nutritive value, or provide a technical function (21 CFR §§172.5 (a)(1) and 182.1 (b)(1)). Of these three criteria, the stanol and sterol esters could only bear a health claim if they were found to provide nutritive value since they clearly do not contribute any of the other three.

The IFT Expert Panel agrees that stanol/sterol esters are components of food that provide health benefits in the same way that dietary fiber is viewed as providing health benefits. The beneficial effects of fiber are based on their physical and physiological effects in the gastrointestinal tract. From the standpoint of nutrient requirements, humans do not require dietary fiber; nevertheless dietary fiber provides benefits of gut motility and cholesterol binding. The cholesterol-lowering effects of the sterol/stanol esters similarly bind cholesterol in the gut to prevent their reabsorption.

Case Study: Cranberries and Urinary Tract Health

In presenting the Agency’s position on permissible claims for cranberries, FDA specified the proper wording for structure/function claims as well as the requirement that a structure/function claim for foods be derived from the “nutritional value” of the food. FDA did not define nutritive value in this example.

In the preamble to the Sept. 23, 1997, final rule on labeling of dietary supplements (FDA, 1997b), FDA used cranberry products’ effect on urinary tract health to illustrate the Agency’s position regarding structure/function claims. FDA noted that the claim that cranberry juice cocktail prevented the recurrence of urinary tract infections was a claim that the product would prevent a disease, and therefore would bring the product under the “drug” definition in § 201(g)(1)(B) of the FDC Act. “. . . However, a claim that cranberry products help to maintain urinary tract health may be permissible on both cranberry products in conventional food form and in a dietary supplement form if it is truthful, not misleading and derives from the nutritional value of cranberries.”

FDA’s example prompted the cranberry industry to propose a structure/function claim regarding the beneficial effect of cranberry on urinary tract health. Although the industry had ample evidence to support such the claim and meet the “truthful and not misleading” standard, the requirement for contributing “nutritional value” remained to be determined. Unfortunately, the cranberry structure/function claim preceded FDA’s determination that the stanol/sterol esters qualified for a structure/function claim. The cranberry industry developed the position that cranberry food products contained “nutritive value” in light of FDA’s broad definition as noted in the preamble to the regulations implementing NLEA (FDA, 1993a), and thus proceeded to make claims regarding cranberry products helping to maintain urinary tract health. FDA did not object to the cranberry claim, implying that the industry’s broad interpretation of nutritive value was acceptable.

Defining Differences in Qualified Health Claims

The IFT Expert Panel supports scientifically defensible health and nutrition messages in the marketplace and therefore supports the concept of qualified health claims. However, consumers may be misled if qualified health claims are not adequately differentiated from approved health claims. To promote consumer understanding, the wording of qualified health claims should clearly indicate the degree of scientific support or certainty associated with a biological effect or modification of disease risk. Both FDA and the International Food Information Council are conducting research to better understand effective consumer messages regarding emerging diet and health relationships. The Expert Panel encourages the Agency to consider the information derived from these studies prior to issuing proposed rules for qualified health claims.

FDA’s interim guidelines for qualified health claims

provide limited language options for claims with varying levels of scientific evidence. The Agency is encouraged to allow flexibility in language, when equivalent language can communicate effective messages that adequately qualify the level of science supporting such claims.

As FDA has indicated, a “weight of scientific evidence” standard, tempered by the “credible evidence” test, should be applied to qualified health claims. Although the Expert Panel supports the use of any health and nutrition claims that are truthful, non-misleading, and consistent with available science, qualified health claims may be inappropriate when the supporting data are inadequate. The IFT Expert Panel recommends that FDA prohibit claims relying on “very limited and preliminary studies” and develop guidelines that protect consumers from limited scientific information. This type of claim has a high degree of uncertainty and may do more harm than good.

The following examples demonstrate how such claims might be worded.

A claim like **“diets high in X may reduce disease risk Y”** would require the current significant scientific agreement (SSA) standard with the totality of the publicly available evidence supporting a substance/disease relationship and SSA among qualified experts that the relationship is valid.

A claim like **“most studies suggest diets high in X**

reduce disease risk Y” would be authorized when scientific data strongly indicate: (1) an effect or a relationship between substance X and disease Y; and (2) a low risk of negative health outcomes if consumers follow this advice. In addition, qualified experts agree that the claim statement is valid.

A claim like **“emerging data indicate diets high in X may reduce disease risk Y”** would be allowed if there are limited data regarding the association between substance X and disease risk Y. These claims also may be modified to include the type of studies that support the relationship (e.g., “only a few epidemiological reports ...”). However, there must be agreement among qualified experts that the claim statement is valid.

In all situations, the claims should not be authorized if following the dietary advice poses a risk of negative health effects.

FDA’s interim system for qualified health claims does not use biological mechanisms. In the past, FDA recognized the value of clinical interventions, epidemiologic and mechanistic research in contributing to the totality of the evidence used to establish a diet and health relationship, both at the Keystone Dialog and in the guidance for claims that meet the SSA standard. FDA is encouraged to incorporate recommendations for mechanistic research in their evaluation system for qualified health claims.

Process for Bringing Functional Foods to Market

The IFT Expert Panel identified a seven step process that would address critical aspects in the design, development and marketing of functional foods (see Fig. 5).

After identifying a potential new bioactive ingredient (Step 1), the ingredient's efficacy and safety must be evaluated (Steps 2 and 3). When selecting an appropriate food vehicle for the bioactive substance (Step 4) one must consider characteristics of the food, the ingredient and the intended consumer. An independent peer review and regulatory oversight (Step 5) ensures the accuracy of health claims, which must be properly communicated to consumers (Step 6). Finally, in-market surveillance confirms the findings of the pre-market assessments (Step 7). Although all seven steps would be undertaken for each new bioactive substance and the resulting functional foods, the specific requirements within each step vary depending upon the physical, chemical and biological characteristics of the functional component, the applicable regulatory requirements and the health claims to be made.

Step 1: Identify Relationship Between Food Component and Health Benefit

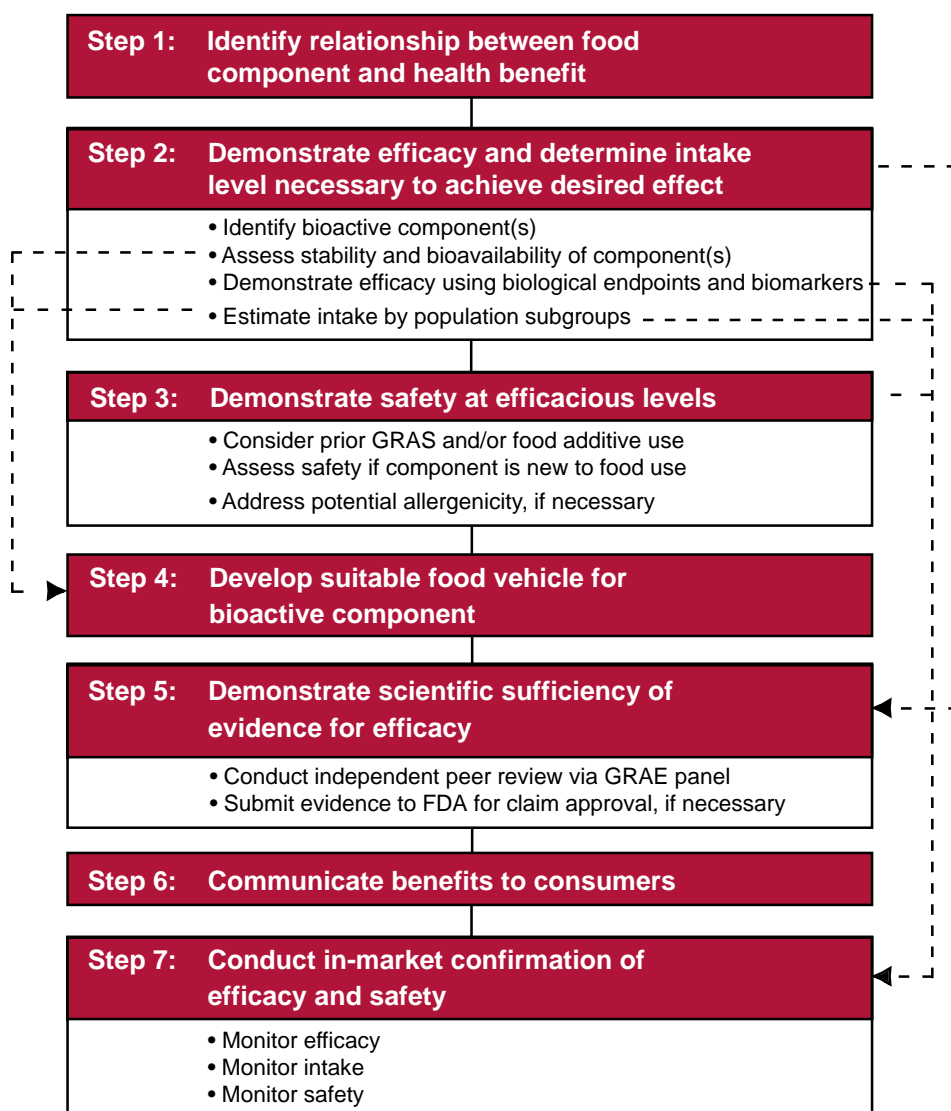
A sound scientific basis for the relationship between functional foods and health benefits is critical. A wealth of scientific literature describes numerous types of research that can identify potential relationships between functional components and health benefits. Once potential links have been identified, rigorous investigations are needed to confirm the initial observations through controlled studies with appropriate test materials.

For example, researchers are intensely investigating several promising bioactive compounds, including plant sterols/stanols and plant phenolics. Multiple epidemiological and case control clinical trials have been conducted for these compounds. The func-

tions of plant sterols and stanols that have been determined from those studies are summarized below (see page 40). Plant phenolics are a large, diverse, and complex group of phenolic compounds including proanthocyanidins, isoflavones, catechins, anthocyanins, flavonoids, phenolic acids (notably cinnamic acid, ellagic acid, and gallic acid) and others. A variety of potential benefits have been identified for these compounds including effects in reducing risk of hypertension, reduced risks of cardiovascular disease as well as the benefits of antioxidants in scavenging free radicals. Additional research is underway.

Other compounds of particular interest include several terpenes and terpenoids (citrus); phytoestrogens and saponins (legumes); glucosinolates (cruciferous vegetables); fiber-including lignans (flaxseed, barley, soy, berries, and

Fig. 5. Seven Steps for Bringing Functional Foods to Market



other fruits/vegetables); and tannins (many plants, apple juice, blackberries, coffee, tea, chocolate, and red wine). Other research is focusing on bioactive peptides (milk, soy, and other proteins) with possible health benefits such as antioxidant activity, blood pressure reduction, and free radical scavenging effects. A vast range of potentially bioactive substances remains to be cataloged and linked to health outcomes.

Step 2: Demonstrate Efficacy and Determine Intake Level Necessary to Achieve Desired Effect

Demonstrating the efficacy of the bioactive component(s) is critical in building a strong scientific basis for claims related to the intake of a functional food. Unfortunately, it is not an easy task.

Identifying Bioactive Components

The ability to identify and quantify the components of interest in functional foods is an important first step in the determination of efficacy. Over the past several decades, the diversity and sensitivity of analytical methods has improved dramatically, and researchers are now able to identify a broader range of substances. In many instances, the specificity of methods has improved considerably. Methods with improved sensitivity, specificity, robustness, and reproducibility continue to be developed. The selection of the most appropriate method (or combination of methods) for a particular analysis depends upon a variety of factors:

- What is being analyzed? Is it a single entity or a group of components?
- Is the whole component of interest or only the bioactive part of the component?
- What are the lowest and highest amounts of an analyte that must be determined?¹¹
- Does the compound exhibit different potencies depending on the chemical form of the compound (e.g., ascorbic acid vs. dehydroascorbic acid; different carotenoids, vitamin E forms, and folic acid (conjugated vs. nonconjugated))?¹²
- Are there matrix effects (e.g., food or fiber) on method performance? and
- Are there food processing effects on the analyte of interest that in turn affect the performance of the analytical procedures?

The method of analysis must be able to accurately measure the compound of interest at the level where the desired or undesired effect is expected. When the compound has the potential for different potencies, accurate and precise measurement is especially important.

In some instances, the bioactive component(s) may be unidentified or partially identified. For example, scientists may know only that the bioactive component(s) belong to the terpene or alkaloid group. In such instances, it may be necessary to analyze the “fingerprints” of several molecules to confirm that the same substances are present when

¹¹ This is especially important for bioactive compounds, whether they offer benefit or have potential to do harm. For example, a bioactive compound may be physiologically relevant at the nanogram level while analytical methodology may permit its detection at picogram levels or lower.

¹² Such situations warrant accurate and precise measurements of a specific component (or group of components) depending on the analyte(s) of interest.

multiple studies are conducted. When researchers have little or no information on the chemical identity of the bioactive compounds, they may use a defined surrogate compound in the efficacy assessment. For instance, the compound(s) affecting a biological response or clinical presentation may be unknown, but a biomarker (e.g., a metabolite or surrogate) that is measurably modulated in response to the ingestion of a functional food might be identified and quantified. In such cases, it is important to establish the correlation between the biomarker, the biological activity and possible clinical significance within a given stage of life, males vs. females, or healthy vs. ill subjects.

Assessing Stability and Bioavailability of Bioactive Substances in Food Matrices

Nutrients and bioactive substances must be stable in the food if they are to be functional at the time of consumption. Advances in food processing technology have provided many techniques for stabilizing nutrients and other valued substances in food. Long-term stability tests must assess the efficacy of bioactive compounds in commercial products. Manufacturers also can use the test results to establish a product shelf life that assures maximum efficacy.

Furthermore, a bioactive substance cannot exert its beneficial effects unless it is bioavailable. *In vivo* physiological utilization of a food component depends on several factors including the physical and chemical form of the component, the effect of the total diet, the effects of food processing, and environmental factors.

Physical Form

When a food component is coated, microencapsulated, emulsified, or altered in some way from its original state, its absorption and utilization may be affected. Even apparently minor physical changes in the food may affect absorption. For example, folate bioavailability from pureed spinach can be higher than from leaf spinach (Catenmiller et al., 2000). Sometimes cooking a food alters absorption of a substance, e.g., absorption of various carotenoids from fruits and vegetables is significantly lower when eaten raw compared to cooked (Boileau et al., 1999; Gartner et al., 1997). Even when the nutrient is administered as a supplement, the form in which the supplement is given can significantly influence the bioavailability of the nutrient. For example, Fuller et al. (2001) demonstrated that the availability of β -carotene administered as water-miscible beadlets was significantly higher than when administered as synthetic β -carotene gelscaps or mixed carotenoid *Dunaliella salina* gelscaps.

Chemical Form

The bioavailability of food components can differ significantly depending on the chemical form in which they are ingested. For instance, iron is more bioavailable from ferrous sulfate or ferrous citrate than from ferric chloride. The ferrous form is more readily absorbed than the ferric form (Fairbanks, 1994). However, in some fortified foods, the ferrous form of iron can cause oxidative reactions in the

food resulting in discoloration and off flavors. Likewise the bioavailability is different for the alpha and gamma tocopherol and for the different species of selenium. Folic acid is best utilized when given as the folate form of the nutrient (Halsted, 1990). Similarly, Deming et al. (2002) have shown that for gerbils the bioavailability of vitamin A isomers changes significantly depending on which isomer is administered. A recent review (Tanumihardjo, 2002) examined the factors that seem to influence vitamin A bioavailability.

Effects of the Total Diet

The other foods consumed in conjunction with a functional food may influence the bioavailability of a food component. In some cases, scientists know that the presence of one substance can affect the absorption of another. For example, a high level of zinc in the diet decreases copper absorption (Fosmire, 1990), while dietary vitamin C increases iron absorption (Olivares et al., 1997). In other cases, the exact reason for the change is not as well known. In an example tied to a particular food, Huang et al. (2000) found that β -carotene bioavailability was reduced by 35% when consumed along with radishes.

Effects of Food Processing

Basic food processing methods (e.g., drying, heating, freezing, fermentation and simple chemical methods, such as salting and smoking) have their origins in prehistoric times and are very effective food preservation tools in use today. Significant developments made in the industrial age include pasteurization and canning/bottling, the former encountering significant resistance and both being indispensable to modern society. The state of the science behind the various sources of food spoilage, including microbial, enzymatic, chemical and physical mechanisms, allows for significant improvements in food processing through both development of novel methods and greater understanding of product formulation, thereby increasing the overall quality of goods produced. Current research efforts are focused on non-thermal, non-invasive processing techniques such as irradiation, high hydrostatic pressure, high intensity pulsed electric field, oscillating magnetic field, light pulses and novel chemical and biochemical methods (Barbosa-Canovas et al., 1998). Despite all these developments, the basic goal of processing remains unchanged, to provide a stable, safe and plentiful food supply. Some of these processes affect the concentrations of nutrients and other bioactive components or the bioavailability. Thus, processing must be considered in evaluating the activity of any functional food.

Fortification is one way in which food processing can alter the bioactive profile of a food. Significant health crises have been resolved via the implementation in 1924 of the addition of iodine to salt to prevent goiter and the 1940s implementation of the additions of vitamin D to milk to prevent rickets and niacin to flour to prevent pellagra. A more recent example is the establishment of the addition of folate to bread and breakfast cereals to prevent neural tube defects in the offspring of women of childbearing age (see

Appendix A for further explanation) (CDC, 1999).

Removal of anti-nutrients to improve nutritional value is accomplished using targeted process techniques. Anti-nutrients are secondary compounds that prevent their counterparts from being digested. For example, phytic acid in grains has been shown to hinder mineral absorption. Processing to remove the bran of grain remedies this situation (Liener, 1994). Other examples include heat destruction of lectins (to prevent adverse reaction) and fermentation or heat destruction of trypsin inhibitors (to improve protein digestibility) in soybeans (Liu, 1997; Savelkoul et al., 1992).

In some cases, knowledge of the different chemical forms of an ingredient is useful to ensure that the desired nutrient value and/or function is achieved in the finished product. Vitamin C (ascorbic acid) is a good example. Vitamin C is a nutrient that acts as a biological reducing agent and is involved in several metabolic functions, including iron absorption, collagen synthesis and immune function. Vitamin C may also be used in foods as an acidulant, an antioxidant to prevent browning or as a flavoring to provide acidic notes. However, oxidation of vitamin C to dehydroascorbic acid during processing, transport, and storage decreases the biological activity, thereby limiting nutritional benefit.

Recent studies have identified the ability for food processing to enhance nutrient availability. Examples of nutrients proven to have such an effect include lycopenes in tomatoes (Gartner et al., 1997), and α - and β -carotenes in carrots (Edwards et al., 2002). In both cases, the processed paste or sauce forms of these raw materials have been shown to provide greater nutrient bioavailability, likely due to physical breakdown of cell walls. Other nutrients under investigation include xanthophylls (Zaripheh and Erdman, 2002), isoflavones (Messina and Barnes, 1991) and lipids (Dunford, 2001).

The need for long shelf life and the desire to meet consumer demands has led researchers to the development of natural compounds for preservation, many of which are also known to provide nutritional benefits. Natural food components such as lecithin (phospholipids) and fatty acids are used as emulsifiers/stabilizers, wetting enhancers and baking improvers and to promote “good” cholesterol in emulsion systems such as beverages and sauces. Anthocyanins are used to provide color as well as for their antioxidant properties. Gums can be used to stabilize/thicken and to boost dietary fiber levels.

Formulation techniques can also be used to enhance product efficacy and/or safety. Prevention of microbial growth and improvement of overall product stability prepares products for abuses from mishandling (e.g., temperature abuse). Formulation techniques range from novel use of preservatives (e.g., essential oils, food acids) to use of humectants (e.g., sugars) to control water activity. Packaging can also be tailored to ensure efficacy and/or safety through incorporation of agents to control the internal package environment, e.g. water activity, pH, or oxygen content or through incorporation of antimicrobials (Grower et al., 2004).

Environmental Factors

Environmental factors during crop production (e.g., soil, rainfall, temperature, pest infestation, use of fertilizers, geographic location) and subsequent handling (e.g., contamination, transportation, storage, processing) can affect both the bioavailability and the absolute levels of many bioactive compounds. For example, selenium content in broccoli is affected by a variety of environmental conditions (Finley et al., 2000). Efficiency of selenium uptake by plants depends on two main factors: soil selenium concentration and chemical form of selenium. Typically, the higher the concentration of selenium in soil, the higher the uptake by the plant. Higher levels of selenium in the plant also can increase the amount of the more bioavailable organic form of the nutrient. In another example, warm temperatures or drought during seed maturation have been reported to increase free α -tocopherol in soybeans (Britz and Kremer, 2002).

Demonstrating Efficacy

Demonstrating the efficacy of functional food components is a complex and costly task, but one that is essential to consumer and regulatory acceptance of functional foods. Although filled with scientific challenges, the efficacy of functional foods can be demonstrated in a science-based process that provides the necessary scrutiny in an effective and efficient manner.

Biological Endpoints and Biomarkers

Reliable measures of the effects of bioactive components of functional foods are critical. In some cases, researchers can directly measure the health or disease prevention endpoint (e.g., frequency of urinary tract infections) or the biological effect (e.g., decreased neural tube defects with increased serum folate levels or serum low density lipoproteins (LDL)/high density lipoproteins (HDL) cholesterol levels as an indicator of cardiovascular disease risk). However, usually researchers must identify a biomarker that functions as a reliable surrogate measure of the underlying biological effects (e.g., improved performance on a physical endurance test). As the case studies beginning on page 35 illustrate, biomarkers can take a variety of forms, ranging from changes in biological endpoints to changes in overt physical performance, which is imputed to relate to underlying biology. In some cases, the biomarker will be a measure of exposure rather than a measure of effect.

Regardless of form, biological endpoints or biomarkers are critical in demonstrating the exposure to and efficacy of bioactive components of food. The International Life Sciences Institute (ILSI) (2002) identified examples of biomarkers (see Table 6). Changes in any of the following functions might be associated with a functional food, measured directly or through the use of an appropriate biomarker:

- physical performance;

- cognitive, behavioral, and psychological function;
- organ or system function (gastrointestinal, genitourinary, bone); and
- chronic disease (heart disease, peripheral vascular disease, diabetes, hypertension, obesity, cancer, degenerative and inflammatory arthritis).

Appropriate biomarkers for disease risk should have three critical features (ILSI, 2002):

- The biomarker should respond appropriately in clinical or diet trials;
- The effects should mirror what had previously been determined in epidemiological trials; and
- The surrogate should reflect a biologically plausible hypothesis.

Researchers face challenges in identifying appropriate exposure biomarkers. Exposure biomarkers should be stable and should directly reflect over a reasonable period of time the intake of the functional food or, preferably, the bioactive component of interest. Exposure to all food components of interest cannot be identified through the use of exposure biomarkers. A recent review of equol's role as a biomarker illustrates the advantages and limitations of using biomarkers (Setchell et al., 2002). Equol is a non-steroidal estrogen formed from daidzein by the intestinal bacteria and excreted in urine. Daidzein is one of the major bioactive isoflavones in soybeans. Equol is superior to soy isoflavones in its antioxidant activity and is relatively more stable than other soy isoflavones. However, not all individuals produce equol because they lack the necessary intestinal bacteria. Consequently, one cannot universally use equol quantification as an index of daidzein utilization or to assess the potential health benefits of soy.

Biomarkers are a specific physical trait used to measure or indicate the effects or progress of a disease or condition. Although scientists have identified many possible biomarkers, few biomarkers have been validated, and many more are needed. (See Appendix B for additional examples.) For a biomarker to be effective, researchers must confirm the relationships between changes in the biomarker and changes in biological function. For example, exposure biomarkers must accurately reflect intake and bioavailability. Surrogate biomarkers are often used as a substitute for biomarkers or when a less specific physical trait is being used to measure an effect or condition.

In the field of exercise performance, three easily measurable and widely accepted functions—strength, endurance, and aerobic capacity—can be assessed as reflective of relative ability to perform certain common types of physical activity. Muscle glycogen can be used as a biomarker for one or more of these functions. Alternatively, surrogates may be used as a measure of physical performance. Strength can be determined by assessing 1-repetition maximums (1RM) and /or number of repetitions possible at some submaximal level of 1RM. Ergometers or free weights are used for these measurements. Maximal aerobic capacity and endurance times at submaximal capacity can be assessed using treadmills or exercise bicycles. These approaches have been used to evaluate the

Table 6. Biomarkers for Well Being and Disease Risk Reduction
(ISLI, 2002)

Physical performance	Muscle glycogen, endurance time trial
Gut function	Gastrointestinal hormones, e.g., cholecystokinin; physical/chemical parameters, e.g., viscosity; biological/physiological responses, e.g., transit time
Immune function	Whole body measures, e.g. delayed hyperactivity
Appetite control	Reduction in food intake, reduction in energy intake, hunger rating profiles
Cognitive function	No conceptual framework; need for markers that represent complexity of real-world decision making
Atherosclerosis	Blood pressure, LDL cholesterol, HDL cholesterol, intima-media thickness
Obesity	Body mass index, measures of fatness
Diabetes	Glucose tolerance, fasting blood glucose, insulin levels
Cancer	Recurrence of colon polyps, aberrant crypt foci
Bone health	Bone density, calcium kinetics

effects of products containing creatine, various amino acids, antioxidants, different carbohydrates (e.g., ribose, glucose polymers), and caffeine (FNB, 2001).

Biomarkers will be especially difficult to identify in the area of cognitive, behavioral, and psychological function because of the difficulty in identifying clearly measurable physical or physiological end points. However, potential surrogates do exist, including testing documents that can be used to evaluate the potential effects of functional foods. These include standard intelligence tests such as Stanford-Binet (2004), Wechsler Adult Intelligence Scale (Wechsler, 1986), Raven's Progressive Matrices (Raven et al., 1965) and others; personality inventories such as the Minnesota Multiphasic Personality Inventory (Greene, 1980); and depression indexes such as Beck's (Beck et al., 1996).

Among other human organs or systems such as gastrointestinal, genitourinary, and bone, some established biomarkers exist as well as many indicators of function and performance that can serve as surrogates to evaluate the influence of functional foods. Readily measured beneficial gastrointestinal functions range from simple records of gastrointestinal symptoms to measurements of gastric emptying time, intestinal transit times, and hormonal (i.e., insulin, cholecystokinin) response to nutrient intake.

In the genitourinary area, functional foods have been promoted for urinary tract (cranberry) and prostate (saw palmetto) health. Biomarkers such as recurrence rates of urinary tract infections, urinary frequency and rates of nocturia are appropriate methods to evaluate the effectiveness of these functional foods.

The prevalence of osteoporosis in the elderly has triggered considerable interest in functional foods that foster bone health. Fortunately, excellent biomarkers are available to assess bone status, ranging from the gold standard—bone mineral density by dual x-ray absorptiometry—to simpler

techniques such as rates of fracture; serum levels of osteocalcin, bone-specific alkaline phosphatase, and vitamin D; and urinary measures of bone turnover (hydroxyproline, pyridinium cross links, or cross-linked N-telopeptides of type 1 collagen).

Criteria for Evaluating Efficacy

Building a strong scientific basis for functional food claims relies on the ability to demonstrate the efficacy of the food's bioactive component(s). Demonstrating efficacy in experimental animals, while not trivial, is quite straightforward. Proving efficacy in humans is substantially more difficult. Most of the epidemiological associations of diet and reduced disease risk relate to overall dietary practices, not a single bioactive component. Linking specific benefits to the consumption of individual foods or specific food components is difficult and requires rigorous scientific protocols. Hill (1971) asked, [when "f]aced ... with a clear and

significant association between some form of sickness and some feature of the environment, what ought we specifically to consider in drawing conclusions about the nature of the relationship, causation or merely association?" The central issue with most observations of diet intake and disease risk is indeed whether the observations can be assigned to cause and effect or to an association of dietary pattern to health outcome.

Hill (1971) proposed specific criteria to use in evaluating research findings (see below), and these criteria have guided the evaluation of diet and health interrelationships for the last two decades. Two key reports in the late 1980s (FNB, 1989; HHS/PHS, 1988) that changed public health recommendations in the United States relied upon Hill's criteria, as did the subsequent Dietary Reference Intake reports from the Food and Nutrition Board of the Institute of Medicine (e.g., FNB, 1997). Some structure/function claims for specific foods have been successfully developed and supported by FDA by following these criteria (see case studies in this report). However, the process has been hampered by limitations in the current regulations and/or government interpretations of those regulations (e.g., the requirement to meet the "nutritive" value stipulation).

Hill's Criteria (Hill, 1971; Keystone, 1996)

Strength of association – how statistically significant and convincing are the data that support the relationship?

Consistency of the observed association – how well do the available data from different sources, areas, and types of studies support the relationship?

Specificity of the association – do the data demonstrate a predictable relationship between the bioac-

tive component and the proposed effect?

Temporal relationship of the observed association

– is the proposed effect observed following treatment with the bioactive component?

Dose-response relationship – do the data demonstrate a magnified effect of the bioactive component with increasing dose?

Biological plausibility – is there a plausible mechanism to explain the effects of the bioactive component?

Coherence of the evidence – does the relationship help explain the available data, when viewed as a whole?

In applying the Hill criteria to the research findings, the IFT Expert Panel believes it is also necessary to consider:

The amount and type of evidence – The amount and type of evidence sufficient to demonstrate efficacy will vary for each functional food component. Therefore, experts in the relevant area of study must determine the data requirements. All forms of competent and reliable scientific research are considered. As a rule, well controlled human clinical studies are the most directly applicable and understood form of evidence and therefore are given the most weight. When a clinical study is not possible, epidemiological evidence may be considered, such as research explaining the biological mechanism underlying the proposed effect. Animal *in vivo* studies are useful, particularly where they are widely considered to be acceptable substitutes for human research or where human research is not feasible. Animal *in vivo* studies also can be used to determine the underlying mechanisms by which the functional food produces its effect. Although no specific number of studies can be set, the replication of research results in an independently conducted study adds to the weight of the evidence.

Quality of evidence – The quality of a study is paramount; evidence for reproducibility and internal validation of quality are critical. The design, implementation, and analysis of results must be conducted in a competent and reliable manner following accepted principles for testing hypotheses. General principles accepted in the scientific community to assure the validity of studies for demonstrating efficacy include: (1) carefully controlled double-blind structure; (2) sufficient duration to establish long-term efficacy; (3) appropriate dosing regimens to document a dose-response relationship; (4) recognized biological or chemical mechanism/biomarker that explains the effect; (5) statistical significance of findings; and (6) results that provide a meaningful benefit for consumers. (Some effects that are statistically significant might only contribute a trivial effect on consumer health.) Where one or more of these cannot be met, qualified experts must consider the impact on the conclusions.

The totality of the evidence – Studies cannot be evaluated in isolation, and all relevant research should be

considered. In fact, the context of the scientific evidence is just as important as the internal validity of individual studies. The studies used to substantiate a claim must be largely consistent with the surrounding body of evidence. Wide variation in study outcomes and inconsistent or conflicting results will raise serious questions about efficacy. Inconsistencies in the evidence must be examined to determine whether plausible explanations exist. In some cases, different results are attributable to differences in dosage, the form of administration, the population tested, or other aspects of study methodology. The contribution of non-dietary factors such as smoking, and environmental contaminants or conditions may need to be evaluated.

The relevance of the evidence to the specific claim – Research supporting efficacy claims must be relevant to both the food product and the specific benefit being claimed. Necessary questions include: How does the dosage and formulation of the proposed functional food product compare with that used in the study? Does the product contain additional ingredients that might alter the effect of the functional ingredient? Is the product administered in the same manner as the ingredient used in the study? Does the study population reflect the characteristics and lifestyle of the target population? If research conditions differ significantly from the use being promoted, additional research may be needed to support extrapolation from study results to claimed effect.

The IFT Expert Panel recommends that evaluation of a functional food's efficacy rely on the Hill criteria. These evaluations must explicitly address the strength and relevance of the data supporting the bioactive component's specific role in improving the health outcome of interest. Companies developing functional foods will assemble the research necessary to determine the efficacy of the proposed product, but independent peer review will confirm the accuracy of the evaluation. This evaluation process applying the Hill criteria will be most effective when undertaken by an independent expert panel as described in Step 5 below (see page 45).

FDA has approved health claims or qualified health claims for the bioactive compounds described in the following case studies. The case studies illustrate how points from the Agency's evaluation would fit into the Hill criteria, if it were to be adopted as the evaluation framework.

Case Study: Efficacy of Omega-3 Fatty Acids

The essentiality of omega-6 fatty acids was established in 1930 (Burr and Burr, 1930). Although the physiological importance of the omega-3 fatty acids and their biochemical involvement in key pathways received scant attention until the 1990s, it is now well understood (Connor, 2000; Holman, 1998; Lands, 2002). Recently, research has focused on the role of omega-3 fatty acids in altering gene expression (Clarke and Jump, 1996).

A substantial body of literature demonstrates that the ingestion of omega-3 fatty acids—typically as the result of consuming fish or dietary supplements—provides a variety of health benefits. Studies of omega-3 fatty acid supplement-

tation during pregnancy support the important role of omega-3 fatty acids in fetal development and during early life (Birch et al., 2002; Makrides and Gibson, 2000; Olsen and Secher, 2002; Simopoulos, 1999). Numerous studies have documented the contribution of omega-3 fatty acid ingestion to improving cardiovascular health, apparently by reducing platelet aggregation, inhibiting inflammation in the intimal lining of blood vessels, and enhancing the HDL/ LDL ratio of circulating lipids (Connor, 2000; Madsen et al., 2001; Simopoulos, 1999; von Schacky et al., 1999). Other reports have suggested that omega-3 fatty acids reduce infectious diseases by enhancing the immune

response (Anderson and Fritsche, 2002), improve mental function (Edwards et al., 1998; Tanskanen et al., 2001), inhibit cancer (Simonsen et al., 1998; Terry et al., 2001), reduce arthritis pain (Cleland and James, 2000; Volker et al., 2000) and prevent cardiac arrhythmia (Nair et al., 1997). The FNB (2002) cited an inverse association between the dietary omega-6:omega-3 fatty acid ratio and both cardiovascular disease and cancer.

Multiple studies have demonstrated the necessary strength of association between consumption of omega-3 fatty acids and specific disease states, although the strength of the association varies by disease (Connor, 2000). The

Table 7. Case Study: Omega-3 Fatty Acids and Coronary Heart Disease (FDA, 1991; FDA/CFSAN/ONPLDS, 2000c; 2004a, b)

Hill Criteria ^a	Evidence Supporting/Against	Studies Cited by FDA in FR Notice/FDA Papers	References
Strength of association: a strong association is less likely to be the result of errors	<p>Evidence against: "Most of the intervention studies that measured LDL cholesterol did not support a relationship between omega-3 fatty acids and reduced risk of CHD either in diseased or general populations." Short-term intervention studies by Finnegan and Woodman did not show a benefit on the CHD risk factors, including blood pressure, that were measured; Hallgren et al. (2001) showed no correlation with fish intake or blood EPA+DHA (eicosapentaenoic acid + docosahexaenoic acid) and acute myocardial infarction (MI).</p> <p>Evidence for: Hu et al. reported inverse correlation between fish consumption and incidence of CHD including CHD deaths and nonfatal MI; Albert et al. reported inverse relationship between whole blood omega-3-fatty acid levels and CHD death; Rissanen et al. reported decrease in acute coronary events for men with the highest quintile of serum DHA+DPA; (docosahexaenoic acid + docosapentaenoic acid). Mozaffarian et al. and Lemaitre et al. showed lower risk of fatal ischemic heart disease with high EPA+DHA but no association with non-fatal MI.</p>	<p>Studies 1991-2000</p> <p>Albert et al., 2002; Finnegan et al., 2003; Hallgren et al., 2001; Hu et al., 2002; Lemaitre et al., 2003; Mozaffarian et al., 2003; Rissanen et al., 2000; Woodman et al., 2002</p>	FDA 10/31/00 letter p 8; 9/8/2004 letters
Consistency upon repetition: association has been observed by different persons in different places, circumstances, and times	<p>"Recent studies have not found beneficial effects on blood lipids from intake of omega-3 fatty acids in normal, healthy persons or in persons at risk for CHD, the same conclusion reached by the Federal government and in other authoritative reports regarding the effects of fish oils on serum lipids."</p> <p>FDA concluded the majority of observational studies consistently observed an associated CHD risk reduction from intake of EPA and DHA.</p> <p>"Definitive evidence on a relationship between omega-3 fatty acids and reduced risk of CHD in the general population was not demonstrated by interventional data."</p>	<p>DHHS, 1988, 1989, 1990; Finnegan et al., 2003; Harris et al., 1990; NRC/NAS, 1989; Woodman et al., 2002</p> <p>Studies 1991-2000</p>	<p>56 FR 60672</p> <p>9/8/2004 letters p 11</p> <p>FDA 10/31/00 letter p 8</p>
Specificity: a specific association is evidence in favor of causality	<p>"None of the studies that reported a relationship between fish intake and CHD distinguished fish consumption from other factors associated with fish consumption. Therefore, it was not possible to determine whether the effects observed were due to omega-3 fatty acid intake or to some other factor associated with fish consumption." Some studies showed the groups with the highest serum levels of EPA and DHA had lower CHD.</p> <p>"Additional study is needed to determine if the omega-3 fatty acids per se in the fish are specifically and causally related to reduced risk of CHD."</p>	From final rule	<p>FDA 10/31/00 letter p 6; 9/9/2004 letters p 9</p> <p>FDA 10/31/00 letter p 11</p>

strength of association is determined largely by the consistency of results in available research reports.

The known biochemical actions of omega-3 fatty acids provides a meaningful biological plausibility for their proposed health effects. The seminal work of Holman (1998) and Lands (2002) established that the two families of unsaturated fatty acids (i.e., omega-6 and omega-3 fatty acids) serve as substrates for enzymes that elongate and desaturate the commonly available precursors (e.g., linoleic acid [C18:2, omega-6] and alpha-linolenic acid [C18:3, omega-3]) to the longer chain and more highly unsaturated versions found predominantly in mammalian phospholipids. These longer chain analogs serve as precursors for formation of the eicosanoids, prostaglandins, and leukotrienes. Eicosanoids produced from omega-3 or omega-6 derivatives are similar in structure but often have opposing physiological effects. For example, eicosanoids derived from omega-6 fatty acids are inflammatory, whereas those derived from omega-3 fatty acids are either non-inflammatory or much

less inflammatory (Shapiro et al., 1993). This understanding of the biological mechanisms provides coherence for evidence that suggests a wide array of physiological effects.

Because omega-3 and omega-6 fatty acids serve as substrates for the same enzyme systems, it is not surprising that the two families of fatty acids compete for these enzymes. As a result, the dietary ratio of omega-6 fatty acids to omega-3 fatty acids influences which substrate and hence which eicosanoid will predominate. Compared to historical intake levels, the Western diet is relatively high in omega-6 fatty acids and low in omega-3 fatty acids. The omega-6:omega-3 fatty acid ratio of Paleolithic diets is estimated at 1-2:1 compared to 20-30:1 in the current Western diet (Simopoulos, 1999). This increased intake of omega-6 fatty acids has induced a relative deficiency of omega-3 fatty acids. In fact, it has been suggested that the ratio should be in the range of 1-4:1 for optimal health (Simopoulos, 2003).

Table 7 below summarizes FDA comments regarding the data that support a dietary supplement health claim for

Table 7. Case Study: Omega-3 Fatty Acids and Coronary Heart Disease, continued

Hill Criteria ^a	Evidence Supporting/Against	Studies Cited by FDA in FR Notice/FDA Papers	References
Time sequence: exposure to causative agent occurs before endpoint of interest	FDA did not specifically address this, but the results of intervention studies support the time sequence.		
Biologic gradient: evidence of a dose-response curve			
Plausibility: association is biologically plausible	“Also, the omega-3 fatty acid content of the fish diet associated with reduced CHD was so low that the importance of omega-3 fatty acids is questionable, i.e., calling into question the biologic plausibility of the relationship.”		56 FR 60672
	“Omega-3 fatty acids showed a reduction of risk for CHD in a diseased population, but the effect is apparently not working through a mechanism of LDL cholesterol reduction.”	Studies 1991-2000	FDA 10/31/00 letter p 8
Coherence of explanation: association is consistent with current knowledge of the disease/endpoint and biomarkers known to be associated with it	“In the 1993 final rule, FDA noted that, although there was evidence for effects of omega-3 fatty acids on clinical measures that may be related to the risk of CHD, such as reduction in fasting and postprandial triglycerides, reductions in platelet aggregation and adhesion, and changes in the composition of lipoproteins, qualified experts did not generally agree at the time that these endpoints were closely related to the risk of CHD.”	From final rule	FDA 10/31/00 letter p 3; 9/8/2004 letters p 11
	FDA concluded that the weight of the scientific evidence for the qualified health claim for EPA and DHA omega-3 fatty acids outweighs the scientific evidence against such a claim and therefore extended the claim to foods in addition to supplements. “The Agency also stated that the data from clinical studies revealed that omega-3 fatty acids had no effect on serum cholesterol, LDL cholesterol, or HDL cholesterol, the blood lipid variables most closely associated with risk of CHD.”	From proposed rule	FDA 10/31/00 letter p 6

^a Friis and Sellers, 1999.

Two additional Hill criteria (experiment and analogy) were not included in the table as FDA did not discuss them in their review of the data for the health claim, and the report from the Keystone Center (1996) did not include them either.

omega-3 fatty acids and coronary heart disease (CHD). Although the FDA review did not refer to the Hill criteria, the organization of the table is intended to facilitate comparisons.

In 1993, FDA refused to approve the health claim, citing a lack of significant scientific agreement and the lack of effect on serum cholesterol, LDL or HDL, the recognized biomarkers for CHD (FDA, 1991, 1993b). In 1999, the U.S. Court of Appeals for the D.C. Circuit in *Pearson v. Shalala* directed FDA to reconsider use of a qualified health claim (164 F.3d 650 (D.C. Cir. 1999)) and the Agency then allowed a dietary supplement claim stating: “Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease. FDA evaluated the data and determined that although there is scientific evidence supporting the claim, the evidence is not conclusive” (FDA, 2000a; FDA/CFSAN/ONPLDS, 2002). In 2004, FDA allowed a similar claim for conventional foods

containing omega-3 fatty acids (FDA/CFSAN/ONPLDS, 2004a, b).

Case Study: Efficacy of Soy Protein

Soy protein has been shown in numerous trials to reduce serum cholesterol in men and women with mild to moderate hypercholesterolemia. The active component(s) of soy protein foods have not been identified, despite extensive research.

Prior to 1995, numerous human trials of very small group sizes had investigated the effects of various soy-based foods on serum cholesterol. Anderson and coworkers (1995) performed a meta-analysis on 38 studies and concluded that substituting soy protein (from isolated soy protein (ISP) or from textured vegetable protein) for animal protein significantly lowered total and LDL cholesterol and triglycerides, without affecting HDL cholesterol. Over the next few years, a number of larger, placebo-controlled, clinical trials

Table 8. Case Study: Soy Protein and Coronary Heart Disease (FDA, 1998j, 1999c)

Hill Criteria ^a	Evidence Supporting/Against	Studies Cited by FDA in FR Notice/ FDA Papers	References
Strength of association: a strong association is less likely to be the result of errors	“In most intervention trials in subjects with total cholesterol <300 mg/dL (milligrams/deciliter), soy protein was found to reduce total and/or LDL cholesterol levels to a clinically significant degree.”	Bakhit et al., 1994; Baum et al., 1998; Bosello et al., 1988; Carroll et al., 1978; Crouse et al., 1999; Goldberg et al., 1982; Jenkins et al., 1989; Kurowska et al., 1997; Mercer et al., 1987; Potter et al., 1993; Van Raaij et al., 1981	63 FR 62989
Consistency upon repetition: association has been observed by different persons in different places, circumstances, and times	“In five of seven well controlled studies of hypercholesterolemic subjects consuming low saturated fat and low cholesterol diets, soy protein intake was associated with statistically significant decreases in total and/or LDL cholesterol levels, either in the entire study populations or subsets of subjects with higher initial blood lipid levels.”	Bakhit et al., 1994; Baum et al., 1998; Crouse et al., 1999; Holmes et al., 1980 (2 trials); Kurowska et al., 1997; Porter et al., 1993	63 FR 62988
	“In all seven intervention studies conducted in adults with type II or familial hypercholesterolemia, large and statistically significant decreases in both total and LDL cholesterol levels were observed in response to consumption of diets containing soy protein.”	Descovich et al., 1980; Gaddi et al., 1991; Lovati et al., 1987; Sirtori et al., 1977, 1985; Verrilo et al., 1985; Wolfe et al., 1981	63 FR 62989
	“Based on the studies reviewed in the soy protein proposed rule and the new studies reviewed in this document [soy final rule], FDA concludes that the totality of the available scientific evidence supports a consistent, if not universal, hypocholesterolemic effect of soy protein included in a low saturated fat and low cholesterol diet. The degree of consistency is notable in light of the different experimental designs and diets studied, the different forms and amounts of soy protein tested, and the variability in initial cholesterol levels of the subjects.”		65 FR 57709
Specificity: a specific association is evidence in favor of causality	“Soy protein was tested in a variety of food forms (as soy beverages, formulated into meat and dairy product analogs, or baked into foods, such as muffins and breads) but produced fairly consistent results regardless of the food form fed and apparent differences in processing techniques.”		63 FR 62989-62990
Time sequence: exposure to causative agent occurs before endpoint of interest	FDA did not specifically address this, but the results of intervention studies support the time sequence.		

verified these conclusions. In one study, mildly hypercholesterolemic men consumed up to 50 grams/day of soy protein, and a dose-response relationship was noted when comparing serum cholesterol reduction after 3 and 6 weeks of feeding (Teixeira et al., 2000).

Although the exact mechanism is unknown, the primary bioactive components in soy are thought by many scientists to be the isoflavones, which have mild estrogenic properties. Many researchers have suggested that the isoflavones genistein, daidzein, and glycitein are responsible for lowering lipid levels. In a 9-week study of both men and women fed with 25 grams of ISP daily with varying amounts of isoflavones, Crouse et al. (1999) found that only ISP diets with higher amounts of isoflavones depressed serum cholesterol. However, removing isoflavones by alcohol washing the soy protein also removes other bioactives such as saponins that may affect lipid metabolism (Erdman, 2000), so the role of isoflavones is difficult to

measure. The isoflavone-rich ethanol extract from soy has not been shown to significantly reduce serum cholesterol, although this fraction may have direct positive effects on the vascular system, such as improving systemic arterial compliance (Nestel et al., 1997). Therefore, some synergy among the components of intact soy protein appears to provide the maximum hypocholesterolemic properties (Erdman, 2000).

FDA reviewed the strength of the relationship between soy protein (containing isoflavones and other bioactives) and lipid reduction. When considered in the context of the Hill criteria, the evidence evaluated by the Agency demonstrates that the Hill criteria were generally satisfied (see Table 8). Although the mechanism of action and the exact bioactive components responsible for cholesterol reduction were unknown, FDA nevertheless approved a health claim for the lipid-lowering capabilities of soy in 1999 (FDA, 1999c).

Table 8. Case Study: Soy Protein and Coronary Heart Disease, continued

Hill Criteria ^a	Evidence Supporting/Against	Studies Cited by FDA in FR Notice/ FDA Papers	References
Biologic gradient: evidence of a dose-response curve	“The intervention studies suggest that a minimum level of approximately 25 g of soy protein is needed to have a clinically significant effect on total and LDL cholesterol levels.”	Bakhit et al., 1994; Baum et al., 1998; Bosello et al., 1988; Carroll et al., 1978; Crouse et al., 1999; Descovich et al., 1980; Gaddi et al., 1991; Goldberg et al., 1982; Jenkins et al., 1989; Kurowska et al., 1997; Lovati et al., 1987; Mercer et al., 1987; Potter et al., 1993; Sirtori et al., 1977, 1985; Van Raaij et al., 1981; Verrilo et al., 1985; Wolfe et al., 1981	63 FR 62989
	“FDA agrees that the available data on the hypocholesterolemic effects of soy protein do not permit a dose-response assessment. However, FDA notes that dose-response data are not required to establish the qualifying criteria for a substance that is the subject of a health claim.”		
Plausibility: association is biologically plausible	“Other comments reviewed various possible mechanisms for the cholesterol-lowering effects of soy protein and some argued that until the mechanism of action of soy protein is clearly established, no health claim should be authorized. FDA notes, however, that such knowledge is not necessarily required for authorization of a health claim.”		64 FR 57709
	“The evidence shows a clear relationship between soy protein and reduced risk of CHD despite lack of a clearly defined mechanism for its effect.”		64 FR 57711
Coherence of explanation: association is consistent with current knowledge of the disease/endpoint and biomarkers known to be associated with it	“It is generally accepted that blood total and LDL cholesterol levels can influence the risk of developing CHD, and, therefore, that dietary factors affecting these blood cholesterol levels affect the risk of CHD.”	DHHS, 1988, 1990; FNB, 1989	63 FR 62979

^a Friis and Sellers, 1999.

Two additional Hill criteria (experiment and analogy) were not included in the table as FDA did not discuss them in their review of the data for the health claim, and the report from the Keystone Center (1996) did not include them either.

Case Study: Efficacy of Stanols/Sterols

Phytosterols, widely distributed in the plant kingdom, significantly reduce serum LDL cholesterol and thus the risk of cardiovascular disease (Law, 2000). The efficacy of phytosterols has been demonstrated in scores of peer-reviewed published studies (Jones and Raeni-Sarjaz, 2001; Ostlund, 2002).

Structurally, phytosterols are closely related to cholesterol. The scientific plausibility for the benefits of phytosterols is well understood. Apparently, phytosterols compete with cholesterol for incorporation of sterols into micelles in the intestinal lumen, interfering with intestinal absorption of cholesterol, both dietary cholesterol and endogenous cholesterol secreted into the intestinal lumen (Jones et al., 2000; Normen et al., 2000; von Bergmann

et al., 1999). Evidence also indicates that phytosterols influence the membrane proteins ABD-G5 and G8 (Berge et al., 2000; Chen, 2001; Hendriks et al., 1999). While the exact mechanism is not clear, the effect of phytosterols in reducing cholesterol absorption is well established (Miettinen et al., 2000; von Bergmann et al., 1999). This reduction in cholesterol influx then reduces cholesterol availability for incorporation into LDL particles (Blomquist et al., 1993; Hallikainen et al., 2000). The interference in cholesterol absorption has been demonstrated in animal studies and in human trials (Jones and Raeni-Sarjaz, 2001; Ostlund, 2002).

Numerous well designed clinical studies have demonstrated the cholesterol lowering properties of sterols and their hydrogenated derivatives, the stanol family of com-

Table 9. Case Study: Stanol/Sterol Esters and Coronary Heart Disease (FDA, 2000c)

Hill Criteria ^a	Evidence Supporting/Against	Studies Cited by FDA in FR Notice/FDA Papers	References
Strength of association: a strong association is less likely to be the result of errors	"In most intervention trials in subjects with mildly to moderately elevated cholesterol levels (total cholesterol <300 mg/dL), plant sterol esters were found to reduce blood total and/or LDL cholesterol levels to a significant degree."	Hendriks et al., 1991; Jones et al., 2000; Maki et al., 1999; and Maki et al., 1999 (1 study); Jones et al., 1999; Weststrate and Meijer, 1998	65 FR 54700-54701
Consistency upon repetition: association has been observed by different persons in different places, circumstances, and times	"Four studies show a relationship between consumption of plant sterols and reduced blood cholesterol in hypercholesterolemic subjects consuming diets within the range of a typical American diet."	Hendriks et al., 1999; Jones et al., 1999, 2000; Weststrate and Meijer, 1998;	65 FR 54692
	"The results of three studies support a cholesterol-lowering effect of plant sterols in subjects with normal cholesterol values."	Ayesh et al., 1999; Pelletier et al., 1995; Sierksma et al., 1999	65 FR 54694
	"Two studies showed a relationship between consumption of plant stanol esters and reduced blood cholesterol in hypercholesterolemic subjects who consumed plant stanol esters as part of a low saturated fat and low cholesterol diet."	Andersson et al., 1999; Hallikainen et al., 1999	65 FR 54695
	"Eight studies show a relationship between consumption of plant stanols and reduced blood total and LDL cholesterol in hypercholesterolemic subjects consuming diets with the range of a typical American diet. Two studies show a relationship between consumption of plant stanols and reduced LDL cholesterol, but not blood total cholesterol, in the same category of subjects consuming diets within the range of a typical American diet."	Miettinen and Vanhanen, 1994; and Vanhanen and Miettinen, 1992 (1 study); Blomqvist et al., 1993; Gylling and Miettinen, 1999; Vanhanen et al., 1993; and Weststrate and Meijer, 1998 (1 study); Hallikainen et al., 2000; Jones et al., 1999, 2000; Miettinen et al., 1995; Nguyen et al., 1999; Vanhanen et al., 1994	65 FR 54696
	"Two studies show a relationship between consumption of plant stanols and reduced blood cholesterol in subjects with normal cholesterol concentrations consuming a typical American diet."	Niinikoski et al., 1997; Plat and Mensink, 2000	65 FR 54698
Specificity: a specific association is evidence in favor of causality	"Given the variability of amounts and of food carriers in which plant sterols and plant sterol esters were provided in the diets studied, the response of blood cholesterol levels to plant sterols appears to be consistent and substantial, except for plant sterols from sheanut oil and ricebran oil."		65 FR 54701

pounds (Jones et al., 2000; Vanstone et al., 2002; Weststrate and Meijer, 1998). A recent study has established the parity of the two families of compounds (i.e., the stanols and the sterols) in lowering LDL cholesterol (Vanstone et al., 2002) as well as the equivalency of free unesterified stanols and sterols in reducing cholesterol. It is clear that sterols and stanols, free or esterified, are equivalent in lowering serum cholesterol levels and in interfering with intestinal absorption of cholesterol (Normen et al., 2000). Table 9 below,

organized by Hill's criteria, summarizes FDA's conclusions regarding the data supporting a health claim for stanol/sterol esters and coronary heart disease. In October 2000, FDA approved this health claim for certain foods and dietary supplements containing plant stanol/sterol esters (FDA, 2000c). FDA subsequently exercised its enforcement discretion to extend the claim to additional foods and also free forms and mixtures of stanols and sterols (FDA/CFSAN/ONPLDS, 2003c). The data have led to the

Table 9. Case Study: Stanol/Sterol Esters and Coronary Heart Disease, continued

Hill Criteria ^a	Evidence Supporting/Against	Studies Cited by FDA in FR Notice/FDA Papers	References
	"Given the variability of amounts and food carriers in which plant stanol esters were provided in the diets studied, the response of blood cholesterol levels appears to be consistent and substantial."		65 FR 54701
Time sequence: exposure to causative agent occurs before endpoint of interest	FDA did not specifically address this, but the results of intervention studies support the time sequence.		
Biologic gradient: evidence of a dose-response curve	Plant sterols "may be more effective in small doses than previously believed."	Mattson et al., 1982	65 FR 54690
	"The investigators observed that the greater the self-reported daily use of the plant stanol ester spread, the greater the serum cholesterol reduction."	Puska et al., 1998	65 FR 54700
	"Consumption of at least 0.8 g/d (grams/day) of free plant sterols, or 1.3 g/d of plant sterol esters, has consistently been shown to lower blood total and LDL cholesterol."	Ayesh et al., 1991; Hendriks et al., 1999; Jones et al., 2000; Maki et al., 1999; and Maki et al., 1999 (1 study); Sierksma et al., 1999; Weststrate and Meijer, 1998	65 FR 54704
	"The Agency was unable to find an intake level lower than 3.4 g/d that consistently showed cholesterol-lowering effects for both total and LDL cholesterol. At least 3.4 g/d of plant stanol esters (equivalent to 2 g/d of free plant stanols) represents an amount that has been shown to be effective in reducing blood cholesterol."	Andersson et al., 1999; Blomqvist et al., 1993; Gylling and Miettinen, 1999; Hallikainen and Uusitupa, 1999; and Vanhanen et al. 1993; Weststrate and Meijer, 1998 (1 study); Hallikainen et al., 2000; Jones et al., 2000; Miettinen et al., 1995; Nguyen et al., 1991; Niinikoski et al., 1997; Plat and Mensink, 2000; Vanhanen et al., 1994	65 FR 54704
Plausibility: association is biologically plausible	"Long ago, plant sterols (beta-sitosterol and related compounds) were found to prevent absorption of dietary cholesterol apparently by blocking absorption of cholesterol in the intestine."	Best et al., 1955; Davis, 1955; Grundy and Mok, 1977; Farquhar and Sokolow, 1958; Farquhar et al., 1956; Jandacek et al., 1977; Lees et al., 1977; Mattson et al., 1977; Peterson et al., 1959	65 FR 54690
Coherence of explanation: association is consistent with current knowledge of the disease/endpoint and biomarkers known to be associated with it	"FDA concluded that it is generally accepted that blood total and LDL cholesterol levels are major risk factors for CHD, and that dietary factors affecting blood cholesterol levels affect the risk of CHD."		65 FR 54686

^a Friis and Sellers, 1999.

Two additional Hill criteria (experiment and analogy) were not included in the table as FDA did not discuss them in their review of the data for the health claim, and the report from the Keystone Center (1996) did not include them either.

approved use of stanols/sterols in foods in several countries (Food Standards, 2001; Official Journal of the European Communities, 2000).

Case Study: Efficacy of Cranberry

The American cranberry (*Vaccinium macrocarpon*) has a rich history of use as one of America's earliest functional foods (Leahy et al., 2001). Native Americans in New England used cranberries extensively in their diet, medicine and commerce. Medically, the berries were used in poultices to treat wounds and blood poisoning, and the plant leaves were used for urinary disorders, diarrhea, and diabetes. Since then, both fresh cranberries and cranberry products, including beverages and sauces, have a long history of food use.

Twentieth century use of cranberries as a functional food has predominantly centered on use in maintaining urinary tract health. Early studies focused on mechanistic research investigating whether drinking cranberry juice might help maintain urinary tract health by acidifying the urine and preventing the growth of urinary pathogens. A number of studies investigated this effect, with equivocal results (Lowe and Fagelman, 2001). The studies that found an acidification effect generally involved single day feedings of large amounts of cranberry products.

In the 1980s, researchers identified microbial anti-adhesion as a potential alternative mechanism. *In vitro* and *in vivo* tests established that cranberry prevented the adhesion of certain pathogens to uroepithelial cells (Ofek et al., 1991; Sobota, 1984). In the 1990s, proanthocyanidins (PACs) were identified as the cranberry components responsible for this anti-adhesion effect (Howell et al., 1998). Cranberry's PACs were found to have unique structures believed to be responsible for the microbial anti-adhesion effect (Foo et al., 2000a, 2000b).

The first well designed, major clinical study on cranberries was a randomized, double-blind, placebo-controlled 6-month intervention trial using a nursing home population of 153 elderly women (Avorn et al., 1994). Biomarkers assayed for urinary tract infections (UTIs) included bacteria in the urine and white blood cells in the urine. Bacteriuria with pyuria was reduced by nearly 50% with consumption of cranberry juice cocktail. Since then, two other well designed intervention trials investigating the impact of regular consumption of cranberry products on the recurrence of symptomatic UTIs have yielded similar results in populations of younger women (Kontiokari et al., 2001; Stothers, 2002).

To date, FDA has not evaluated this diet and health relationship nor has the Agency taken any enforcement action against companies making structure/function claims regarding cranberry consumption and maintenance of urinary tract health.

An independent group based in the United Kingdom, the Cochrane Collaboration, has evaluated the clinical studies regarding this relationship (Jepson et al., 2004) as part of its stated mission "to help people make well-informed decisions about healthcare by preparing, maintaining and

promoting the accessibility of systematic reviews of the effects of healthcare interventions." Jepson et al. (2004) conducted a comprehensive review of all randomized or quasi-randomized controlled trials of cranberry juice/products for the prevention of UTIs in susceptible populations, including men, women or children. Seven trials (four cross-over, three parallel groups) met the inclusion criteria. Six trials evaluated the effectiveness of cranberry juice, and two trials investigated the effectiveness of cranberry tablets (one trial evaluated both juice and tablets). The authors concluded that some evidence from two good quality randomized controlled trials indicated that cranberry juice may decrease the number of symptomatic UTIs over a 12-month period in women. However, no clear evidence proved effectiveness in children or the elderly. Relatively high drop-out rates suggested that long-term adherence to the treatment may be a problem. In addition, the studies did not provide any guidance as to the optimum dosage or method of administration (e.g., juice or tablets), and further trials were needed, the authors concluded.

The Cochrane reviews did not evaluate the totality of the data and did not address mechanistic plausibility.

A considerable body of mechanistic studies indicate cranberries possess bacterial anti-adhesion properties, preventing certain pathogens from adhering to the urinary tract epithelium, a prerequisite for infection. Clinical research suggests that urine retains the anti-adhesion property for as long as 10 hours after consumption of cranberry juice cocktail. The proanthocyanidins in cranberry have a unique structural feature (A-type linkage) believed to be responsible for this effect. While no dose-response studies have been published, effective doses can be deduced based on the amount of cranberry solids consumed daily in the trials conducted to date. Given that two good quality, randomized controlled trials documented an approximate 50% reduction in recurrent UTIs in various populations of women, the IFT Expert Panel believes a detailed, systematic review using the Hill criteria is warranted to better understand this diet and disease relationship.

Estimating Dietary Intake

To achieve a health benefit, a bioactive substance must be consumed in adequate quantities to achieve the desired effect.

In theory, the calculation of dietary intake for a nutrient or bioactive substance is simple and straightforward. The amount of each food, beverage, dietary supplement, and drug consumed is multiplied by the concentration of the substance of interest in each product. The resulting intake from each product is then summed to estimate total intake. In practice, however, dietary intake assessments are often associated with a significant amount of variability and uncertainty. Variability arises as a result of natural variation in the levels of the bioactive compound in different lots of the food, variations in the methods of preparation, and in the amounts consumed. Uncertainty stems from the complex and variable nature of the data sources used to estimate intake and the inherent variability in consumers' behavior

and biological response to dietary components.

It is often difficult to quantify error factors for data on the content of substances in specific foods, the bioavailability of those substances in various food vehicles, and the amounts of each food consumed by different population segments. Nevertheless, public health programs based on the application of available dietary intake information (such as food fortification, food safety assessments, and dietary guidance) have been very successful. Appendix C provides a historical perspective and overview of food composition databases and the limitations of these data.

Increasing or decreasing the consumption of a nutrient or bioactive substance has both efficacy and safety implications. Evaluating the impact on safety and effectiveness requires quantitative knowledge about intake by the target population, potential high consumers, or population subgroups with special risks or benefits. The target population may be the total population or a segment of the population (e.g., the elderly, women of childbearing age, adult men).

As technology improves, foods designed for specific population groups are likely to enter the market. Therefore, evaluation of intake by the target population may need to determine if significant numbers in that group are either low or high consumers of the designated food(s) or food components. For example, if a large percentage of consumers in the target population do not eat the foods planned for fortification or eat only small amounts, modifying other foods may be more beneficial.

Determining the safety of changing the levels of a nutrient or bioactive substance in the diet of a given population requires information on intake distribution within that population. Assuring that segments of the population do not consume unsafe levels also requires knowledge of the safety of the substance at those levels of consumption. (See Appendix A for information on sources of food consumption data and for a detailed case study on FDA's use of consumption data to decide which foods to fortify with folic acid and what fortifications levels to use).

Step 3: Demonstrate Safety of the Functional Component at Efficacious Levels

In general, the safety of functional foods should be based on the long-standing principle that foods are safe. Further, the safety assessment should accept the safety of components already considered through pre-established programs such as generally recognized as safe (GRAS) substances and approved food additives (see Appendix D).

That said, an objective, science-based evaluation process must establish that functional components are safe at their projected use levels. The scope of potential new functional foods is extremely broad, and the safety assessment framework should be effective for many types of functional ingredients over a broad range of consumer intake levels. The safety assessment must be sufficiently flexible to consider the many factors associated with consumer responses to food and food ingredients, including genetic predisposition, age, sex, nutrition status, and lifestyle.

The nature of the ingredient and the sensitivity of subgroups of the population should be considered. For example, if the functional food is to be consumed by pregnant women, then appropriate reproductive evaluations should be conducted. In unusual circumstances, a product label may need to provide specific information for sensitive population subgroups about differential responses (e.g., a hypoglycemic agent and diabetics).

To be defensible, a safety determination must rely on studies conducted using generally recognized scientific procedures and principles. Although some data may be proprietary during the review process, the findings of the review and the rationale for the conclusions should be thoroughly documented and available for public review at the time the product is put on the market. In-market surveillance (see Step 7 below, page 46) will provide additional confirmation of safety.

Safety Assessments for GRAS Ingredients and Food Additives

When an ingredient is categorized as either GRAS or an approved food additive, and there is reliable information about the substance's potential for pharmacokinetic properties and bioavailability in the intended food matrix, safety assessment may be limited to estimating the range of intakes among consumers before and after introduction of the new food. If the intake among consumers with the highest estimated intakes is similar before and after introduction of the new food(s), little additional evidence of safety may be required.

Guidelines for Safety Assessments

The basic principles of safety testing are detailed in Appendix D and summarized below. The most appropriate safety assessment for a functional food ingredient will be determined on a case-by-case basis. Typically, the safety assessment will include the following:

- documented history of food use (if not a new chemical entity);
- estimates of current and proposed intakes of the functional component(s) (intake/consumption should be estimated for the general population and by age and gender, including estimates on days when the food is actually consumed (e.g., "eaters only") and consumers who are likely to consume higher than typical levels (e.g., 90th percentile consumption). Intake estimates should be realistic and not overly conservative.); and
- toxicological/safety assessment of new intake levels.

Substances without a prior history of safe use will require a comprehensive and critical review of the scientific literature on the biological effects of the ingredient and on chemically related substances. Based on an initial review, specific studies will generally be required to define:

- bioavailability - likely modes of action *in vivo*;
- estimated half-life *in vivo*;
- estimated dose-response for a range of potential effects;
- known pharmacologic/toxic effects;
- evidence of allergenicity; and

- toxicity and safety (human, experimental animals, *in vitro* systems including microorganisms, cells in culture, micro arrays).

Appendix D describes examples of toxicity testing required by FDA for food additives. The safety assessment will vary depending on whether the component will be present at micronutrient or macronutrient levels. The requirements also will depend on the mode of action of the active component and its toxic effects.

When the bioactive component(s) of a functional food are not known (e.g., cranberries), epidemiological studies demonstrating the safety of the whole food would be an important part of the safety assessment.

Use of Epidemiological Data

Epidemiological studies can confirm relationships between dietary patterns and biomarkers or disease occurrence. In some cases, epidemiological studies begin with disease-free subjects and survey lifestyle patterns before disease develops. Although these prospective studies avoid recall bias and the problems associated with selecting controls, they are extremely expensive. Typically, prospective studies evaluate potential risk factors for common diseases. Epidemiological studies have been extensively used to relate diet intakes to the occurrence of heart disease or cancer.

People eat foods, not isolated ingredients, so food intake studies cannot directly assess the intake of a specific bioactive component. Therefore epidemiological studies combine the food intake data with other data to estimate the intake of the substances of interest. Food composition databases are used, but many bioactive components have not been well characterized and quantitative data for such components may be very limited or nonexistent. In addition, isolating the effect(s) of a specific food or nutrient can be difficult because the substances are consumed in combination and may have synergistic effects.

The validity of any dietary assessment tool depends on the individual's ability to recall their diet and to accurately report portion size and frequency of intake. Most epidemiological studies rely on food frequency questionnaires (FFQs) to assess average intake over an extended period of time ("usual diet"). FFQs are easy to administer and process, even in very large studies. However, FFQs may have significant measurement errors from underestimating and/or overestimating intakes of some foods and the necessary grouping of foods into categories.

Allergen Management

Food allergies are abnormal (heightened) responses of the immune system to components of certain foods (Taylor and Hefle, 2001). The components of foods that elicit these abnormal immune responses are typically naturally occurring proteins in the foods. Foods contain millions of individual proteins, but only a comparative few of the proteins have been identified as allergens. Whether naturally occurring or added in product formula-

tions, all proteins that elicit an allergic response warrant special attention. Functional foods are no exception, unless the allergenic component of the food has been reduced or eliminated.

Food allergies are associated with a wide variety of symptoms, ranging from mild and annoying to severe and life threatening (Taylor and Hefle, 2001). The symptoms can involve the gastrointestinal tract, skin, or respiratory tract. The nature and severity of the symptoms experienced by a food-allergic individual may vary from one episode to the next depending on the dose ingested, the degree of sensitization at the time of the episode, and other factors. The only accepted treatment for food allergies is to avoid the offending food.

Any new protein in a functional food should be evaluated for potential allergic reactions. While no single test can perfectly predict the potential allergenicity of a novel protein from a source with no history of allergenicity, the application of a series of tests provides reasonable assurance that the novel protein is not likely to become an allergen.

Manufacturers are required to follow good manufacturing practices and labeling regulations for all foods containing known allergens. Congress has recently directed FDA to publish regulations that require food labels to specifically identify the presence of major allergens (U.S. Congress, 2004).

Step 4: Develop a Suitable Food Vehicle for Bioactive Ingredients

The goal of this phase of development is to select a suitable food vehicle that is appropriate for the intended consumer and delivers the bioactive ingredient at the desired levels. Selection of a food vehicle depends on its acceptability, the stability and bioavailability of the bioactive ingredient within the food, and the consumption and lifestyle practices of the intended audience.

Selection and development of the appropriate food vehicle is an important step to the total success of a functional food. The effectiveness of a functional food is a combination of its efficacy and consumer compliance. Efficacy is the extent to which a bioactive ingredient accomplishes its intended function, and compliance is the degree to which the intended consumer adheres to its recommended usage (Davidsson and Nestel, 2004). Consumer compliance is key to a functional food's success. If an ingredient is consumed at a level well below that recommended, it will be ineffective. Alternatively, if consumed in amounts much greater than intended, it may become toxic.

Bioactive ingredients challenge product developers because they often possess disagreeable sensory and/or physicochemical characteristics. For example, omega-3 fatty acids (commonly sourced from fish oils) and soy proteins both have unpleasant flavors and aromas that are difficult to mask, especially in the quantities necessary to provide a health benefit. Fortunately, new food technologies can address many of these issues. For example, microencapsula-

tion techniques have allowed the addition of omega-3 fatty acids to breakfast cereal and dairy-based products (Berry, 2002). Successful soy products include yogurts, soy-milk products, smoothies and breakfast cereals. The extreme tartness of cranberries presented a similar sensory challenge. After producers modified their flavor and expanded their uses, cranberries are now found in a large variety of juices, baked goods, breakfast cereals and sauces (Berry, 2002). Dried cranberries are also becoming more popular. The high lipid insolubility of sterols and stanols initially limited their compatibility with many food products, but esterification has allowed them to be incorporated into fat-containing foods, such as butter-like spreads and chocolate.

The bioavailability of the micronutrient delivered by the food vehicle was a key aspect of traditional fortification efforts (Hurrell, 2002), a concern that also applies in functional food development. As discussed in Step 2, bioavailability depends on several factors, including the chemical and physical form of the bioactive substance, the impact of other dietary components, food processing effects and environmental factors. The food vehicle should provide a stable environment that will preserve the bioactive ingredient in its desired bioavailable form.

Selection of the food vehicle also must address the characteristics of the target audience. For example, adults with elevated cholesterol levels are the target for sterols and stanols that reduce blood LDL levels, so these substances should be added to foods regularly consumed by this target population. If a functional food were being developed for children, the appropriate food vehicles might be very different.

As noted in the introduction to this report, functional foods lie at the low cost, high consumer participation end of the delivery options continuum and thus may be especially advantageous in lieu of a drug regimen. Many consumers are averse to drugs and may accidentally or purposely avoid taking their prescriptions (Gottlieb, 2000). Consumption of food does not carry such an aversion and is looked upon much more favorably. Functional foods are an effective way to deliver beneficial agents and should become an integral part of public health programs aimed at reducing disease risk.

Step 5: Demonstrate Scientific Sufficiency of Evidence for Efficacy

As described in the section on regulatory standards, all functional food labeling must be truthful and not misleading. Claims for the benefit of a functional food must be based on scientific evidence of safety and efficacy and should be confirmed by appropriate independent experts.

Independent Peer Review

The IFT Expert Panel believes the evaluation of efficacy and safety will be most effective and cost-efficient if it is undertaken by panels of independent experts with appropriate scientific expertise. This approach has been successfully applied to GRAS determinations for many substances. A parallel process should be used to confirm the efficacy

findings for a functional food.

Establishing an independent expert panel to make a generally recognized as efficacious (GRAE) determination would encourage public confidence while conserving government resources. As envisioned by the IFT Expert Panel, GRAE panel reports (accompanied by relevant scientific literature and data) would be submitted to FDA under a GRAE notification process described below. The material submitted would be available for public review, and the composition of the panel would be fully disclosed.

The GRAE panel would be composed of respected scientists qualified to determine efficacy of the component under consideration. The multi-disciplinary nature of the panel would provide a broad context for data and assure that the resulting conclusions are scientifically defensible and relevant to consumer practices. The GRAE panel would use the Hill criteria to determine if the proposed claims are supported by the available evidence.

GRAE panels could be assembled and managed in a variety of ways as long as the composition of the group is fully disclosed and the panel's independence is assured. GRAE panels could be organized by a professional organization, by a private consulting organization, or by the company developing the functional food (provided the panel is given complete autonomy).

Regulatory Approval When Necessary

The process for obtaining approval to market a new functional food will vary based on the nature of the functional component and the proposed claims. In the United States, functional foods are currently regulated under several different sections of the food law as described beginning on page 15. Other countries impose their own specific requirements.

As envisioned by the IFT Expert Panel, FDA would consider the comprehensive GRAE report as part of an orderly process similar to that used for GRAS notifications. FDA should establish a notification procedure whereby any person may notify FDA of a determination that a particular use of a substance is GRAE. FDA would evaluate whether each submitted notice provides a sufficient basis for a GRAE determination and whether information in the notice or otherwise available to FDA raises issues that lead the Agency to question whether use of the substance is GRAE. Following this evaluation, FDA would respond by letter to the notifier within a specified time frame (typically 90 days). FDA could respond in one of three ways:

- The Agency does not question the basis for the notifier's GRAE determination;
- The Agency concludes that the notice does not provide a sufficient basis for a GRAE determination (e.g., because the notice does not include appropriate data and information or because the available data and information raise questions about the efficacy of the notified substance); or
- The Agency has, at the notifier's request, ceased to evaluate the GRAE notice.

If FDA does not reply within the specified time frame, it

would be presumed that the Agency does not question the basis for the GRAE determination and the product could proceed to use the proposed claims.

Step 6: Communicate Product Benefits to Consumers

Once a science-based claim is validated, that information must be communicated to consumers. If consumers are uninformed about the potential benefits of functional foods, few will purchase and benefit from the foods, and the food industry will have little incentive to develop new functional foods.

This communication must establish meaningful connections between the attributes of functional foods and the health-related consequences of consuming those foods (Wansink, 2001). Regulatory policies must allow food manufacturers to accurately characterize a functional food's health benefits and the science supporting those claims. All parties must ensure the messages describing these relationships are properly understood by consumers. Consumer research regarding understanding and perceived benefit is crucial. As knowledge develops, it must be communicated fully, clearly, and in a timely manner. The food industry, health professionals, educators, government officials, and the media can provide this information to consumers through a variety of health messages.

The results of Steps 1-5 should form the basis of consumer messages about the benefits of functional food consumption. Currently, the information on food labels represents a body of carefully reviewed scientific literature on nutrition and health. Consequently, the health-related claims on food labels form an excellent foundation for consumer education on dietary components for health.

In addition to the food label as a communication tool, the media play an important role in communicating scientific developments and fostering consumer awareness of new food components. To guide such communication, the International Food Information Council (IFIC), with IFT and other associations, developed "*Guidelines for Communicating the Emerging Science on Dietary Components for Health*" (summarized below), which address challenges in communicating information about emerging science to consumers (IFIC Foundation, 2004).

Guidelines for Communicating the Emerging Science for Dietary Components for Health

Enhance public understanding of foods, food components, and dietary supplements and their role in a healthful lifestyle. *Serve up plain talk about food and health.* Advise consumers that dietary components are not magic bullets that work alone, but may promote good health when included as part of a healthful diet and lifestyle.

Clearly convey the differences between emerging and consensus science. *Scientific research is*

evolutionary, not revolutionary. Tell consumers where new findings fall on the research continuum and within the overall body of evidence.

Communicate with accuracy and balance.

Carefully craft your communications. Advise a healthy skepticism for potentially misleading headlines, such as "medical miracle" or "scientific breakthrough." Suggest looking beyond dramatic language to get the full story. Explain that facts are facts, but experts may differ in opinion about how to interpret them. Present a complete picture of a study's results, rather than select findings.

Put new findings into the context needed for an individual to make dietary decisions. *Make your messages meaningful.* Translate the latest research into what is on the consumer's dinner plate. Spell out to whom new findings apply and what impact, if any, the findings should have on eating habits.

Disclose all key details about a particular study. *Cite the specifics.* Discuss the study design to help the public understand research results and their validity.

Consider peer review status. *Point out peer review* as a key measure of a study's credibility, although it is not the only key. A credible research study is not a guarantee of conclusive results—it is one piece of a larger puzzle made up by the overall body of evidence.

Assess the objectivity of the research. *When assessing a study's objectivity, consider the facts—* including not only disclosure of funding sources, but also peer review, methodology, and conclusions.

Step 7: Conduct In-market Surveillance to Confirm Efficacy and Safety

The term "in-market surveillance" (IMS) refers to the process of obtaining information on the effects of the functional ingredient after it has been introduced into the marketplace. IMS can confirm the conclusions reached during pre-market evaluations regarding safety and efficacy by monitoring actual consumption patterns and the impact on consumers' dietary patterns and determining if there are any adverse health effects (complaints) that were not identified in pre-market testing.

In limited situations, IMS may be required by regulatory agencies. An IMS program should be a part of an ongoing monitoring program for new highly fortified functional foods. However, an IMS program may be inappropriate in other situations, such as when claims are made for foods already widely consumed (e.g., cruciferous vegetables and their impact on cancer). The most appropriate type of IMS program must be determined on a case-by-case basis.

An IMS program may be active or passive. In active IMS, a sponsor, typically the food manufacturer, engages an appropriate professional group to systematically poll consumers regarding intake patterns. The sponsor may elect to share the information with the appropriate regulatory agency. An active IMS program also may include additional research to further evaluate tolerability or efficacy or to address scientific questions that arose after marketing. In the case of an acute effect (e.g., folic acid), such studies may be feasible. However, in many cases, especially when the desired effects are only seen over the long term, such an active IMS program may be unrealistic.

Passive IMS involves the collection, documentation, and evaluation of complaints about the product (e.g., organoleptic, possible contamination), and may include reports of adverse health events. Frequently, a passive IMS program consists of placing a toll-free telephone number or Internet-access information on the label of the product containing the ingredient in question. The importance of such systems in confirming safety has been proven by almost 50 years of experience in the pharmaceutical industry. Although the information obtained from passive IMS cannot establish a causal relationship between the ingredient and the alleged adverse health effect, these programs remain very useful by documenting trends over time and identifying unanticipated effects that may require further evaluation.

Goals of an IMS Program

The goals of an IMS program include two important tasks: monitoring that the intended intake has been achieved and evaluating the efficacy of the functional ingredient.

As part of IMS, the use practices of consumers should be monitored. Knowing that the substance is available in appropriate amounts in the diet, tests can assess the extent

to which the substance is being absorbed and utilized. If the substance or its metabolite can be measured in the blood or other body fluid, then a study measuring samples from consumers may be useful in assessing exposure by providing evidence of consumption levels and the bioavailability of the substance.

Once intake has been established, studies can assess the efficacy of adding the substance to the diet. Depending on the nature of the condition, the function being addressed, and the substance being added to the diet, long-term studies may be necessary to establish efficacy. Establishing the baseline prevalence of the condition in the population at the time the substance is introduced makes it possible to demonstrate change if the substance is effective. Sometimes an existing national survey such as the National Health and Nutrition Examination Survey (NHANES, see Appendix A) can be used to collect clinical, biochemical, and dietary data. Alternatively, a large clinical trial can collect the necessary data. Ideally, such a study should be a double-blind design so the results are less subject to potential bias.

Conducting such studies is difficult, time consuming and costly. The prevalence of the condition affected by the functional ingredient may complicate IMS. If the prevalence of the condition is low, specialized databases may be necessary to monitor change. Some databases are currently available, including the National Disease Register. If no database monitors the prevalence of the condition, then a special database must be developed. Control subjects who are consuming pre-market levels of the functional component may be difficult to locate, particularly if the component is added to foods that are widely consumed (e.g., folic acid fortification). Despite its potential usefulness, the practical realities of conducting such long-term research may make it nearly impossible to complete.

Role of Research

Emerging science clearly indicates that the functional foods currently on the market represent a small fraction of the possible products. The scientific literature reports almost daily on new insight into the role of existing nutrients, advances in identifying bioactive compounds and their health benefits, and the intersection of genomics and nutrition science in personalized nutrition. Additional research is needed in many areas to ensure that this emerging science continues to be valid and is rapidly translated into consumer-relevant products. All elements of society stand to benefit from this undertaking.

Scientists in academia, government and the private sector are all stakeholders in the continuum of research, from basic exploratory *in vitro* studies to clinical application of findings. The challenges are enormous: the need for a continuous supply of scientific hypotheses, researchers with the curiosity and ingenuity to pursue these hypotheses, and funding to support the entire effort. At the same time, funding for research is limited, both within the government and private sectors. Scientific hypotheses are vetted through internal review within the private sector and through grant review boards and study groups for government funding. Regardless of the venue, the review results are judged relative to value of investment.

Functional foods and molecular nutrition represent novel scientific paradigms that challenge traditional nutrition approaches. The risk of adhering rigidly to current paradigms is that health benefits from a broader approach to diet and nutrition will be slow to arrive on our plates. Speeding the arrival of these health benefits requires innovative and paradigm-shifting approaches to nutrients and their role in health, and funding to expand the knowledge base of molecular nutrition.

As we move into the era of nutrigenomics and individualized diets, protecting the privacy of individuals may become an issue. A legal, ethical and societal framework must be developed to ensure genetic information about food and disease is appropriately handled.

Early stage research is funded largely through government grants at universities or within the government laboratory system at the National Institutes of Health and the U.S. Department of Agriculture, while private sector funding takes the lead as scientific advances are translated into commercial products. Although early-stage expenses may be considerable, commercialization of a functional food product requires substantial incremental investment. Without a period of exclusivity during which companies can earn a reasonable

return on their investment, the private sector is unlikely to commit the resources necessary to develop a wide range of product choices representing the best that nutritional science and functional foods have to offer.

Types of Research Needed

The IFT Expert Panel has identified the areas below as vital to the development of functional foods and worthy of research funding.

Nutrients and Bioactive Substances

Continued basic and applied nutritional research must pursue a more precise understanding of the mechanisms of action for known nutrients, their dose-response relationship, the clinical outcomes and individual variations in response. Diverse health effects are both known and suspected for many nutrients, such as selenium, vitamin E, carotenoids, and the B vitamins. For example, an extensive review of specific nutrient effects on various enzymatic processes by Ames et al. (2002) summarizes only a portion of the scientific inquiry underway to elucidate roles for “standard nutrients.” While a comprehensive review of these studies is beyond the scope of this document, clinical nutrition journals regularly publish studies exploring the role of known nutrients in health.

Potential and actual health benefits of bioactive food components represent a similar frontier in diet-health research. Guhr and LaChance (1997) reviewed the potential roles in health for phytochemicals, including sulfur compounds in cruciferous vegetables, polyphenols in teas, and flavonoids in wine, blueberries, and pomegranate.

Epidemiological studies have repeatedly demonstrated that better health and lower incidence of chronic disease is associated with higher intake of whole grains and multiple servings of fruits and vegetables. These beneficial effects cannot be explained by traditional nutrients alone. *In vitro* research has demonstrated diverse roles for bioactive compounds in blocking, reversing or interfering in molecular level processes, which, if left unchecked, would lead to various chronic diseases (Guhr and LaChance, 1997). Continuing research must identify bioactive compounds and determine their mechanisms of action and effects on health, and this knowledge must then be verified through well designed preclinical and clinical studies.

New and Existing Biomarkers

In functional food research, biomarkers are usually biological endpoints that directly correlate with health status or with exposure to specific food components (exposure biomarker) (see page 33 for additional information about biomarkers). Surrogate markers relate directly to disease development and can be used in place of a

disease endpoint. In reality, scientists have very few well defined and accepted biomarkers or surrogate markers. Some of the accepted surrogate markers include elevated low density lipoproteins (LDL)-cholesterol, elevated homocysteine or C-reactive protein for increased risk of coronary heart disease, the presence of colon polyps for increased risk of colon cancer, and decreased bone mass for increased risk of osteoporosis.

Many physiological measures are of interest to scientists and consumers as possible indicators of health status. Some of these physiologic measures include inflammatory markers (e.g., cytokine levels and C-reactive protein), blood lipids (e.g., triglyceride level and specific fractions, such as high density lipoproteins (HDL)-cholesterol), blood glucose, plasma insulin, satiety hormones, changes in short-term memory, weight loss or weight maintenance, mood alteration, homocysteine levels, and iron status.

Identifying specific cause-effect relationships between dietary components and health is challenging and, in some cases, controversial because of the complexity of human biology and physiology. Biomarkers and their relationship to health status are often identified through observational studies or correlations. At best, correlated factors may suggest a complex, multi-factorial relationship among diet and health and may be supported by scientific theory that appears credible; at worst, the correlations are the result of another unrelated factor and have no basis in fact.

Scientists need to identify additional biomarkers that signal changes in health status and then determine the meaning of changes in those biomarkers relative to a defined health condition. In addition, exposure markers are needed to assess intake, bioavailability and utilization of potential functional food components. The relationship between genes and gene products and disease risk is an emerging area that must be pursued. The effects of diet on biomarkers and the entire human body must be validated through prospective clinical trials.

An expanded database of surrogate markers and exposure biomarkers is essential for these biomarkers to become accepted in medical practice.

Food Vehicles for Bioactive Ingredients

The food vehicle is critical to the overall success of a functional food because it plays an important role in consumer compliance. Additional research should identify and tailor foods for delivery of bioactive ingredients. The criteria for such research should include:

- provision of a stable environment for the bioactive ingredient;
- knowledge of the interactions between the bioactive ingredient and other ingredients in the vehicle matrix;
- maximization of the bioactive ingredient's health benefit;
- maintenance of the bioavailability of the bioactive ingredient; and
- desirable sensory/organoleptic characteristics.

In addition, packaging can contribute to stability, bioavailability and organoleptic quality (Lutter and Dewey, 2003). Research will help scientists better understand each of these issues in functional food development.

Food Composition and Dietary Intake Databases

The value of epidemiological studies in establishing diet and health relationships is well recognized. Retrospective cohort studies using dietary intake databases such as the National Health and Nutrition Examination Surveys (NHANES) can be useful in identifying relationships between diet and health. In fact, dietary intake databases helped establish that diets high in fruits and vegetables reduce the risk of certain cancers. Expanding existing food composition databases also will facilitate this work. The Nutrient Data Laboratory at USDA's Agricultural Research Service has recently undertaken an effort to publish peer-reviewed food composition databases on nutrients with emerging benefits, such as carotenoids (<http://www.nal.usda.gov/fnic/foodcomp/Data/car98/car98.html>), flavonoids (<http://www.nal.usda.gov/fnic/foodcomp/Data/Flav/flav.html>), and proanthocyanidins (<http://www.nal.usda.gov/fnic/foodcomp/Data/PA/PA.html>). The IFT Expert Panel supports efforts to expand USDA food component databases and to update existing databases as better analytical methods become available. It is equally important that the government continue to fund and support the National Center for Health Statistics NHANES research on health status and dietary practices.

Nutrigenomics and Function of Bioactive Components

The intersection of genomics and molecular nutrition presents opportunities to understand nutrient effects and individual variability in response to diet; this understanding has the potential to revolutionize diet, nutrition and food products, and health care. With the unraveling of mouse and human genomes, the stage is set for rapid advancement. Identification of diet responsive genes and single nucleotide polymorphisms must be followed by clinical validation that dietary intervention modifies gene expression towards a healthy phenotype. Such clinical data will improve the validity of conclusions regarding the role of dietary practices on health status.

Nutrigenomics may disrupt established ways of thinking about nutrition, food, the value chain of the food industry, and the role of industry in health care. Mass customization—the ability to provide nutrient plans and products based on the interaction of genetics and diet for groups and individuals—will soon be scientifically possible. However, such products are well beyond the food industry's current infrastructure and business model. This new paradigm raises legal and ethical questions based on development and handling of personal genetic data and changes the boundary between foods and drugs from a clear line to a continuum. Meeting these challenges will require new regulatory paradigms and new food industry and health care value chains.

Policies Regarding Ethics, Regulatory, and Legal Implications of Nutrigenomics and Molecular Nutrition Research

Appropriate privacy of genetic information and limitation of decisions that can be made based on knowledge of an individual's genetic profile has been discussed and debated (Human Genome Project Information, 2004). Until recently, such discussions focused largely on pharmaceutical applications. However, nutrigenomics has brought the issue into the food arena, and the need for potential policies is being explored (Genome Canada, 2004). The IFT Expert Panel supports efforts to develop a legal, ethical and societal framework to facilitate personalized nutrition while safeguarding consumer privacy.

Molecular nutrition research has established a drug-like role for nutrients, and nutrigenomics renders the effect specific for an individual or group of individuals with particular genetic profiles. However, current food regulatory frameworks do not readily accommodate drug-like effects from nutrients and/or personalized nutrient plans based on genetic testing. Drawing on experience with drug development, FDA must develop policies and practices that facilitate the identification of therapeutic effects of foods and enable commercialization of such products.

Expanded Incentives for Health and Nutrition Research

Appropriate incentives to the food industry would greatly enhance the development of functional foods. The research required for a functional food to meet scientific standards for efficacy is a substantial investment, but the return on that investment is not exclusive to that company. As soon as the health claim is adequately documented, competing companies can use the claim.

Various groups have examined the issue of incentives for encouraging additional health and nutrition research. The Keystone National Policy Dialogue on Food, Nutrition and Health (1996) presented at least four concepts for incentives to the food industry:

- Confidential lead-time prior to public notification, giving petitioning organization an initial market advantage;
- Period of market exclusivity after public notification, giving petitioning organization a temporary monopoly on the market;
- Royalties paid by others to use newly authorized claims, giving petitioning organization an additional revenue source; and
- Reduced research costs via incentives, providing exclusivity, additional tax credits, and government research

grants to organizations pursuing health claims research.

FDA's Food Advisory Committee established a Research/Economic Incentive Working Group (IWG) to examine the Keystone incentives and to pursue additional opportunities. The IWG recognized that FDA cannot provide economic incentives for health claim development and noted that legislative action may be needed to provide meaningful incentives to industry.

The IFT Expert Panel believes that the efficacy of functional foods and claimed benefits must be scientifically supported and believes that patents alone are inadequate as economic incentives because:

- A wealth of hard data and speculation in the public domain describes the role of food in health, complicating and/or precluding patent protection that would be broad enough to be commercially meaningful; and
- Patentability may not ensure commercial insulation sufficient to afford investment recovery and reasonable profit.

A system of economic incentives for companies willing to commercialize emerging nutritional science could have broad ranging effects, from the quality of science developed to whether products are commercialized at all. The lack of exclusivity of health claims encourages companies to limit research and use a structure/function claim instead of an approved health claim. Structure/function claims are more limited and often cannot accurately convey the health effects to consumers.

The IFT Expert Panel believes that appropriate incentives for the food industry would enhance our understanding of the health effects of food and diet, leading to extensive improvements in consumer health. Possible incentives such as exclusivity, marketing lead time, and confidentiality should be explored. FDA could encourage health claim development by assisting the company in quickly entering the marketplace with a newly authorized health claim. Utilization of authoritative statements via the FDA Modernization Act of 1997 (e.g., whole grain and potassium health claims, nutrient content claim for choline) has helped provide some marketing advantage in the immediate time period following the approval. Legislative bodies should aggressively pursue tax deductions and credits for health and nutrition research.

In addition, to better leverage government and industry investments, the IFT Expert Panel encourages the food industry to support funding for cooperative research, maybe initially as a pilot program within FDA or USDA. Canada's National Sciences and Engineering Research Council could serve as a model of a program in which industry dollars are matched by government dollars to conduct relevant, peer-reviewed research.

Conclusions

Developing functional foods to improve public health requires contributions from ongoing basic and applied research and modifications to the current regulatory framework to facilitate the review of new functional components and their health claims. The IFT Expert Panel believes the following recommendations are particularly critical to the continued development of functional foods.

Expand research into traditional nutrients, other bioactive food components, and the intersection of genomics and molecular nutrition. Continued basic and applied nutritional research must further explore the roles and mechanisms of action for traditional nutrients. In addition to traditional nutrients, other bioactive food components with the ability to improve health must be identified and their efficacy proven. The intersection of genomics and molecular nutrition presents opportunities for more definitively understanding diet and health in individuals and population groups, with the potential for personalized diets for optimal health.

Expand research on biomarkers and physiological endpoints. Additional biomarkers that signal changes in health status are urgently needed, and the meaning of changes in those biomarkers must be clearly demonstrated relative to a defined health condition. Research is needed to expand the validated biomarkers of health status including assessing how genes and gene products relate to disease risk.

Use generally recognized as efficacious (GRAE) panels to evaluate health claims and streamline the regulatory approval process. Good science is the foundation for health- and nutrition-related claims. A GRAE panel composed of scientists with in-depth knowledge of the particular subject area would use the Hill criteria to evaluate the evidence and prepare a publicly available, comprehensive report of their findings. FDA implementation of the GRAE concept would provide a more predictable regulatory process. Because the GRAS notification procedure implemented in 1997 has proven to be both effective and efficient, FDA should establish a similar procedure whereby a GRAE report would be received and reviewed. FDA would evaluate whether each submitted notice provides sufficient basis for a GRAE determination and would respond to the notifier within a predetermined time frame.

Allow product labeling and health claims to accurately reflect the scientific data without triggering drug status. Attempts to avoid classification as a drug have resulted in misleading (if not outright false) statements of the underlying science. Enormous public health benefits would result from having consumers clearly understand and act on the accurately claimed product benefit.

Modify the current definition and application of the term “nutritive value.” Given the current interpretations of applicable statutes and advancements in nutritional sciences,

it is appropriate to replace “nutritive value” with a more inclusive definition: that benefits for functional foods should be based on nutritive value or through the provision of a physical or physiological effect that has been scientifically documented or for which a substantial body of evidence exists for a plausible mechanism.

Allow health claims based on significant scientific agreement (SSA) and qualified health claims based on the weight of the scientific evidence (WOSE). The ultimate success of functional foods will depend on delivering bioactive components in a predictable and assured manner to effectively reduce the risk of disease and/or improve body structure or function. To achieve this goal, FDA should allow health and nutrition claims that are truthful, non-misleading, and consistent with available science, including qualified health claims. To this end, SSA and the WOSE approaches are valuable assessment methods. While application of WOSE must be tempered by the “credible evidence” test, FDA should not allow claims when the scientific basis is extremely limited and supported only by preliminary studies.

Indicate the degree of scientific certainty for approved and qualified health claims. Appropriate qualifying language should clearly indicate the degree of scientific support or certainty associated with a biological effect or modification of disease risk. FDA’s interim guidelines for qualified claims provide limited language options for claims with varying levels of scientific evidence. The Agency is encouraged to allow flexibility in language, when equivalent language can communicate effective messages that adequately qualify the level of science supporting such claims.

Develop incentives for companies to invest in functional food research and development. The lack of exclusivity of health claims discourages companies from investing in functional food research. Incentives such as a period of exclusivity or tax incentives would encourage food companies to pursue functional food development as a profitable venture.

Use health claims on food labels as the foundation for consumer education regarding dietary components for health. Consumer education is an important component of the success of functional foods. Accurate claims on food labels help consumers select products that satisfy their desire to promote self-care and improve health. All food communicators, including food scientists and health professionals, must work together to improve consumer education by accurately characterizing new scientific developments.

Achieving the potential benefits of functional foods requires contributions from basic and applied scientists in academia, government and industry. Consumers want and need these products, and mechanisms must be developed to ensure that the next steps are undertaken now to foster their availability.

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Appendix A: Food Consumption Databases

Scientists have been studying human food intake for centuries. These studies were conducted for logistical reasons (e.g., planning provisions for military expeditions), nutrition studies, or other health reasons.

Most of the early studies used observational techniques, i.e., the participants are observed while being served and consuming the food. By definition, such studies are classified as prospective studies. In most cases, data are collected on what was consumed and in what quantities. In some observational studies, the observation is not evident to the subject, and the amount consumed is measured accurately. Although highly accurate, observational studies are labor intensive and thus generally useful only with small groups of people. As such, observational studies are impractical in deriving estimates of food consumption for large population segments or the population as a whole.

Surveys are an alternative approach for estimating food consumption by large population segments. In this approach, a statistical representation of the population is surveyed on food consumption by interviewers or via questionnaire. By definition, these studies are retrospective studies.

The accuracy of data derived through the use of food consumption surveys depends on many factors (Anderson, 1986; Dwyer, 1994; FNB, 1986), foremost of which is obtaining a representative sample of the study population that achieves an adequate sample size and a high response rate. The necessary sample size is often dictated by the diversity of the population's food habits. The accuracy of the data also depends on the skill of the interviewer; quality of the instrument used; adequacy of instructions; and age, education, memory, and commitment of the respondents. Finally, data coding and processing also can be a major source of error. Incorrect identification of a food or its ingredients can significantly alter the estimated intake of a nutrient or bioactive substance. In recent years, the use of laptop computers for data collection has lowered or eliminated errors in coding and the transfer of data during processing.

Alternately, participants may be asked to create a food record over a period of time. These prospective studies have some advantage in that data collection is not dependant on the participant's memory.

For a variety of needs, the federal government began conducting interview surveys to determine what foods the population was consuming. The U.S. Department of Agriculture (USDA) started consumer studies of "household food use" in 1935 with the use of a 7-day food recall list (Hegsted, 1982). These surveys were conducted again in 1942, 1948, and 1955 (USDA, 2002a). During 1965-1966, USDA repeated the 7-day household food use survey and, in addition, FDA funded a 24-hour dietary recall of individuals

in each household during one quarter of the study. During 1977-1978, USDA conducted a 7-day household food use survey that included a 24-hour recall and a 2-day diet record of all individuals in each household funded by FDA. The survey was designated the Nationwide Food Consumption Survey (NFCS). During 1985-1986, USDA conducted a special survey of women between 19 and 50 years and young children between 1 and 5 years of age. That study is called the Continuing Survey of Food Intakes by Individuals (CSFII). The participants were interviewed in person for a 24-hour dietary recall and were then asked to participate in 5 additional nonconsecutive 24-hour dietary recalls by telephone. During 1987-1988, USDA conducted the second NFCS survey that was identical in design to the 1977-1978 survey (7-day household food use, 24-hour recall, and 2-day diet record of all individuals). During the 1989-1991 CSFII USDA survey, household members were interviewed for a 24-hour diet recall and were asked to provide a food record for the following 2 days. During the 1994-1996 CFSII USDA survey, selected household members were given two nonconsecutive 24-hour dietary recalls. In the 1998 CFSII USDA survey, two nonconsecutive 24-hour dietary recalls were secured for children less than 10 years of age.

The Department of Health and Human Services' National Center for Health Statistics (NCHS) began conducting a series of health and nutrition examination surveys in the late 1960s. The first survey was conducted in ten states that were considered to have some of the highest levels of malnutrition and was called the Ten State Survey (CDC, 1972). The main focus was to investigate the occurrence of clinical symptoms of malnutrition, but a dietary component also was part of the study. This was the first large-scale study of a U.S. population in which clinical symptoms of malnutrition were linked to dietary intake. The procedures had previously been perfected by U.S. and Canadian scientists and used in many poorer countries around the world in the 1950s (NIH, 1963). NCHS then conducted three National Health and Nutrition Surveys (NHANES I (1971-1975), NHANES II (1976-1980) and Hispanic HANES (1982-1984)) in which a 24-hour dietary recall and food consumption frequency questionnaires were used (LSRO, 1989; Murphy and Michael, 1982;). During 1988-1994, NCHS conducted NHANES III in which a 24-hour dietary recall was administered together with questionnaires on food consumption frequency and dietary supplement use (LSRO, 1995). During 1999-2001, a survey designated as Continuous NHANES was conducted in which a 24-hour dietary recall was administered together with questionnaires on food consumption frequency and dietary supplement, antacid, and medication use. This study was jointly conducted by NCHS and the Agricultural Research Service (CDC/NCHS, 2002).

In 2002, the CSFII and the dietary component of NHANES were integrated. The dietary intake methodology developed by USDA and the sampling and data collection capabilities of NCHS were combined to create a survey that would more easily link diet and nutrition data to health status data. In contrast to CSFII, data for the combined survey will be collected continuously instead of periodically.

In the USDA Household Food Consumption Survey and the NFCS and CFSII surveys, the respondents were requested to provide a description of the portion size of all the foods consumed. The same procedure was followed for the NHANES surveys conducted by NCHS, except that in some studies, food models were used to help consumers describe the portion size. Since this information is dependent on memory, such estimates are subject to significant random error.

There is also random error associated with the time the surveys take place. It is common for individuals to eat different portion sizes of the same food on different days and at different times of the year. Interviewing a sufficiently large population has minimized the size of this random error. Studies have shown, however, a systematic bias toward under-reporting of total energy consumed (Mertz et al., 1991). Another concern has been that these databases may distort information on the frequency of consumption of some individual food items.

Data from the National Eating Trend Survey (conducted by a commercial firm) are another source of information on the frequency of consumption of many food items. This survey employs large numbers of households to keep long-term records of all foods consumed by each member in the household. These records are periodically combined to provide a relatively current database from which changes in eating trends can be obtained.

The USDA CFSII and NHANES surveys provide abundant databases from which information on the distribution of dietary intake can be derived for the total population and for a wide number of demographic segments of the population. These data are critical to assessing the effectiveness and the safety of adding additional amounts of a nutrient or bioactive substance to the diet of the entire population or specific population segments.

Folate Fortification Decision: Range of Dietary Intakes and Associated Issues

The addition of folic acid to many cereal products is an excellent example of how data from the nutrient databases and food consumption surveys has been used to implement a public health measure. Research on the occurrence of neural tube defects (NTD) provided strong evidence that women who consume additional folic acid prior to conception and during early pregnancy had a lower risk of a NTD birth. Neural tube defects are serious birth defects that can result in infant mortality or serious disability. Because the level of folic acid in the food supply was adequate to meet the recognized nutritional needs of the population, this addition-

al folic acid served a non-nutritional function. Furthermore, excessive folic acid intake could negatively affect individuals with vitamin B-12 deficiency by masking megaloblastic anemia. If untreated, this deficiency can result in permanent peripheral neuropathies (FDA, 1993c).

FDA first had to determine the level of dietary folic acid that was needed by women of childbearing age. Research data were not available to demonstrate the quantity of folic acid necessary to prevent NTDs among the U.S. population so the Agency adopted the U.S. Public Health Service recommended level of 400 microgram (mcg) per day as the desired minimum (USPHS, 1992). Based on evidence in the scientific literature and expert opinion, FDA established a dietary intake of 1 milligram (mg) of folic acid per day as the safe upper limit.

The Agency then faced the task of identifying the fortification scenario that would achieve the greatest increase in the dietary folic acid intake for women of childbearing age without exceeding the safe upper limit of any population segment. FDA used a database from a 1987/1988 USDA survey to establish the distribution of food intake for different population segments and a special database on the folic acid composition of foods. In addition, general information on the use of dietary supplements was used to assess their contribution. The baseline intake of all population segments was calculated, and the mean baseline consumption levels were then used to determine the additional folic acid needed to achieve the 400 mcg dietary intake goal for women of childbearing age. These data also were used to calculate distributions of folic acid intakes for age/sex population groups.

The same data revealed the most effective vehicle(s) for implementing fortification. More than 90 percent of women of childbearing age consumed cereal-based products on a daily basis. Other potential vehicles were milk or certain juices. Using the distribution data sets, alternative fortification options were calculated. One scenario was to add 70 mcg of folic acid per 100 grams (g) of cereal-grain products. Another possibility was to add 140 mcg of folic acid per 100 g of either milk or selected juice products. The cereal product fortification option was superior in reaching the greatest number of women of childbearing age.

Having identified cereal products as the most useful fortification vehicle, the next task was to determine the most effective safe level of folic acid to be added to these products. Calculations were made to determine the total amount of dietary folic acid that would result from additions of 70, 140, and 350 mcg of folic acid per 100 g of cereal products. These calculations were made for both low and high consumers in the following age and sex groups: males and females 1 to 3 years; males and females 4 to 10 years; females 11 to 18 years; females 19 to 50 years; females 51 years and over; males 11 to 18 years; males 19 to 50 years; and males 51 years and over.

The estimates from these calculations indicated that at the 70 mcg level, low consumers in the target population (women of childbearing age) would only achieve approxi-

mately half of the recommended folic acid intake if they were taking a dietary supplement. At the 70 mcg level, the high consumers in subgroups of 51 years and over would consume between 450 to 550 mcg/day without dietary supplements and between 770 to 790 mcg/day with dietary supplements. Estimates of folic acid intake at the 140 mcg fortification level indicated that low consumers in the target population would consume more than half the recommended 400 mcg folic acid level and 240 mcg with a dietary supplement. At the 140 mcg folic acid fortification level, high consumers among adults 51 years and over would consume 800 to 840 mcg with dietary supplement use. Finally at the 350 mcg folic acid fortification level, low consumers in the target population would consume between 360 to 370 mcg of folic acid per day with dietary supplement use, but all consumers 11 years and older would have folic acid intakes in the range of 680 to 980 mcg without supplement use and 970 to 1,180 mcg with supplement use. With dietary

supplement use, high consumers among 1 to 3 years and 4 to 10 years would consume between 670 mcg and 1,030 mcg, respectively.

After carefully considering these estimates, FDA concluded that the addition of folic acid at a level of 140 mcg per 100 g of cereal grain products was the best fortification option. The 140 mcg/100 g cereal product level was adopted in a proposed regulation for public comment and was established in a final rule after considering all comments submitted to the proposal (FDA, 1996b).

Similar procedures are now used to consider both the public health benefits and the upper limit safety risks for the addition of other substances to the food supply. Population specific intake data coupled with food composition data provide a scientific basis for balancing potential health benefits and risks. These procedures also are used to evaluate the safety of other food additives that provide some functional role in food processing, stability, distribution, or food acceptance.

Appendix B: Additional Examples of the Effects of Functional Components of Foods

A number of functional foods including soluble fiber (Nicolosi et al., 1999), plant sterols (Thurnham, 1999), and polyunsaturated and monounsaturated fats have been shown to favorably influence cholesterol levels.

More recently, it appears that many chronic disease conditions including heart disease (Ridker et al., 1997), peripheral vascular disease (Ridker et al., 1998), diabetes (Arnalich et al., 2000), obesity (Visser et al., 1999), and certain cancers (Barber et al., 1999) may be chronic inflammatory conditions. Therefore a biomarker for inflammation is needed. C-reactive protein, a protein made by the liver in response to inflammatory or infectious stimulation (Bistrian, 1998) has been proposed. For instance, the poorer the glycemic control in diabetes, the higher the C-reactive protein and the poorer the outcome (Stehouwer et al., 2002). The usual upper limit concentration of C-reactive protein in normal subjects is 8 mg/L, and levels in poorly controlled diabetes and obesity exceed that.

A new highly sensitive test for C-reactive protein, which includes the usual normal range of 1-8 mg/L, has been shown to mark coronary artery disease risk (Rader, 2000). Subjects in the highest quartile for this highly sensitive C-reactive protein have nearly a tripling of risk for coronary artery disease when compared to those in the lowest quartile (Ridker et al., 1997). Furthermore, recent studies show that half of the benefit of statins to reduce coronary artery disease risk comes not from the lowering of cholesterol but from the lowering of C-reactive protein levels (Nissen et al., 2005; Ridker et al., 2001; Ridker et al., 2005). It may be that C-reactive protein is actually a biomarker for underlying biological changes. Levels of C-reactive protein may be affected by infectious diseases and other confounding conditions that would complicate the interpretation of C-reactive protein levels as a measure of effects of functional foods.

Soy has a history of use as food in many regions of the world. However, although both the safety and efficacy of soy foods in lowering circulating cholesterol has been documented, ongoing research on other potential health effects of soy and soy constituents suggests that we must remain cautious in increasing these active components in Western diets. In particular, data on cancer prevention by soy and soy constituents is less convincing. Case-control epidemiological studies suggest that soy foods or other plant-based foods in the Asian diet are associated with lower cancer rates (Birt, 2001). Some epidemiological studies suggest that while some soy-based foods such as tofu were associated with reduced rates of cancer in Asia, others (such as fermented soy foods) did not seem to possess this

property (Birt, 2001). Prospective or intervention studies assessing the ability of soy foods in cancer prevention have not been conducted.

There is considerable interest in the role of isoflavones in the prevention of breast cancer with some investigators suggesting that early life exposure to dietary soy may be particularly important in preventing this disease in animal models. In contrast, animal investigations and recent human studies suggest that isoflavones or soy foods may actually increase the growth of breast cancers (Birt, 2001; McMichael-Phillips et al., 1998). This was not surprising because of the known estrogenic activity of isoflavones. Indeed, recent reports have suggested that women with breast cancer should avoid isoflavone-rich foods such as soybeans (de Lemos, 2001).

Two areas of considerable interest for assessing the value of functional foods are obesity and cancer. Obesity has become epidemic in the United States and the world in general. Although there are multiple causes of obesity, including increased food intake and reduced energy expenditure, there is still considerable controversy about the role of other factors such as the ratio of fat to carbohydrate. In addition, there is considerable recent interest in the role that the glycemic index (the relative insulin response to a given amount of dietary carbohydrate intake) may play in increasing the prevalence of obesity (Ludwig, 2002; Willett et al., 2002). Some researchers have proposed that the higher the intake of high glycemic index foods, the greater the risk of obesity and the so-called insulin resistance syndrome (Ludwig, 2002; Willett et al., 2002). If valid, measuring the glycemic index of foods and assessing insulin resistance by simple measures such as the insulin sensitivity index (fasting glucose/fasting insulin) could be appropriate biomarkers for assessing the role that functional foods may play in obesity.

An authoritative review of the available literature by the American Diabetes Association (ADA) (Sheard et al., 2004) concluded that at this time, there is insufficient information to determine whether there is a relationship between glycemic index or glycemic load of diets and the development of diabetes. The efficacy of the glycemic index on overall blood glucose control indicates that the use of this technique can provide an additional benefit over that observed when total carbohydrate is considered alone. However, since much of the risk of developing type 2 diabetes is attributable to obesity, maintenance of a healthy body weight is strongly recommended as a means of preventing this disease. ADA concluded that the relationship between glycemic index and glycemic load and the development of type 2 diabetes remains unclear at this time.

The assessment of immune function and its relationship to the risk of infectious disease and chronic illnesses such as cancer has also been considered in the evaluation of functional foods. The tests commonly employed to assess immune function illustrate the earlier points made about biomarkers. Isolated lymphocytes or peripheral blood mononuclear cells can be used to assess rates of transformation or production of cytokines when stimulated by mitogens or endotoxin. The putative effect of functional foods would be to increase this reactivity albeit within the normal range. Similarly, another sensitive measure of immune function is the delayed hypersensitivity skin response that

measures the response to the intradermal injection of common recall skin antigens like candida, trichophyton, and mumps. In this case, an effective immune-enhancing functional food should produce a larger response. As in other measures, virtually all healthy subjects will have reactivity within a “normal” range and consumption of the functional food would shift the reactivity to a more favorable level. Of course, it is not a foregone conclusion that increased responsiveness is necessarily beneficial under all conditions. Under certain conditions, heightened reactivity might increase the risk for allergic disorders (Braun-Fahrlander et al., 2002).

Appendix C: Food Composition Databases

For more than a century, scientists have been developing chemical and biological methods for quantifying substances in foods (Hepburn, 1982). The resulting data have been used to assemble extensive public and private databases for use by government, industry, research institutions, and health practitioners. These databases are periodically revised to reflect new information derived from improvements in analytical methods, changes in levels of substances in foods, and changes in food production and processing that affect food composition.

Historical Perspective

In the last 30 years, government agencies have expended considerable effort on developing criteria for data in food consumption databases (Hepburn, 1982; Hoover and Perloff, 1981). The recommendations of the White House Conference on Health and Nutrition held in 1969 (Mayer, 1969) brought attention to the issue, and the data requirements for assessing the safety and adequacy of the U.S. food supply provided added impetus. Initiatives to improve consumer diets by providing more nutritional information also emphasized the need for improved data. In the early 1970s, a group of federal agencies agreed that a consolidated food composition database would be beneficial. As a result, FDA funded a contract to develop the initial program to computerize the database then known as USDA (U.S. Department of Agriculture) Handbook 8. FDA also adopted a compliance policy that encouraged industry to submit data on food products to the USDA database, with the assurance that such data would not be used for regulatory purposes. The federal agencies also took steps to coordinate efforts to improve the quality of data being generated.

Improving official analytical methods was a significant task. The complex chemical matrices of many foods made it difficult to isolate and quantify nutrients and other bioactive organic compounds. In addition, modern analytical methods could improve both the precision and accuracy of the analysis for many nutrients and other substances. Therefore, extensive resources were devoted both by government and industry to conduct collaborative studies for the purpose of establishing improved Official Methods of Analysis under the auspices of the Association of Official Analytical Chemists (AOAC) (Stewart, 1980, 1983).

Another important step was to establish criteria for identifying and selecting the food samples to analyze. A probability-based analysis was used to establish guidelines for the number of samples, the size of the samples, and

number of collection sites required for each sample. A database for a given nutrient required more samples of foods high in that nutrient compared to foods containing lesser amounts of the nutrient. Finally, the criteria addressed evidence that geographical location and time of the year influenced nutrient levels.

In 1990, Congress established the National Nutrition Monitoring System (U.S. Congress, 1990). Under this system, federal agencies have reaffirmed support for the Nutrient Databank System (NDBS) maintained by USDA's Agricultural Research Service. Currently, the NDBS contains data on more than 113 components in more than 6,000 foods. It also contains several composition data sets for specific food constituents based on more limited numbers of foods. For example, data sets are available for individual carotenoids, isoflavones, trans fatty acids, and vitamin K (USDA, 2002b). The databases contained in this databank are the main foundation for nearly all public and private databases available in the United States and many international databases as well.

Adequacy of the Data

Several factors affect the adequacy of the NDBS data sets for use in a particular dietary intake and exposure assessment. The first and foremost question is whether the NDBS contains adequate data on the nutrient or bioactive substance; data on many substances of interest are not currently included. Other specialized food composition databases cover certain types of substances such as lipids, pesticides, and heavy metals. If an adequate data source is not available, a special analytical program must derive the data.

Additional analytical studies also may be needed if the nutrient or biologically active substance is listed but an additional amount is added to a food to achieve the desired functional effect. Existing food composition databases may not be appropriate if:

- The data were obtained from plant or animal species that are no longer being produced, and new species that have higher or lower levels of some nutrients or biological substances are now being used;
- The plant source was produced in a new location where environmental effects change its composition;
- New processing techniques affect the food's composition; or
- The food was derived from a plant that was modified using recombinant DNA (rDNA) biotechnology to intentionally raise or lower the level of a nutrient or bioactive substance (IFT, 2000).

In all of these situations, additional analysis should be conducted to meet the criteria of the NDBS data sets. These criteria are available from the USDA Nutrient Data Laboratory (Holden and Patterson, 2003).

Appendix D: Safety Testing for Substances Without Prior History of Safe Use

Many substances in food are considered safe based wholly or in part on the empirical evidence from long periods of consumption, i.e., prior history of safe use. In the absence of a prior history of safe use, potential new functional ingredients must be evaluated for safety prior to introduction into the food supply.

The safety evaluation of new functional ingredients should adhere to the same safety testing principles used for other substances and should reflect the intended use levels (The Redbook (FDA/CFSAN/OFAS, 2004), OECD guidelines (2004)). The safety evaluation should encompass both the functional ingredient and functional food(s).

The basic principles of safety testing include:

- The exposure conditions during testing must simulate human intake conditions;
- The ingredient tested must be the item of commerce in the form that will be ingested;
- Dose-response relationships must be established;
- A no observed adverse effect level (NOAEL) should be determined in each study;
- Human data should be generated as soon as possible in the testing program;
- Studies should be designed to conserve resources without compromising the scientific merit of the studies;
- Appropriate comparative data are critical for proper interpretation of the results;
- The extent of required testing is a function of the nature of the chemical ingredient and the extent of intake, including level and duration; and
- Generally accepted guidelines for testing are recommended (e.g., OECD, Redbook).

Experts determine the amount of toxicological data necessary to assess the ingredient's safety. After critically evaluating the available information and identifying gaps, they develop a study plan. The scope of testing necessary is a function of the nature of the chemical ingredient and the extent of intake, including level and duration. Potentially sensitive subsegments of the population (e.g., children, diabetics) and the potential allergenicity of the ingredient receive special consideration.

Generally, scientists must choose between two basic approaches to safety assessment, the matrix and tier approaches.

Matrix Approach. The matrix approach consists of a complete battery of standard tests. The tests are conducted as proposed, and then the results are critically evaluated and used to establish acceptable daily intake (ADI) and other relevant end points.

Tier Approach. In contrast, the tier approach is a step-based approach based on a logic tree. The tier approach can conserve resources because data are critically evaluated after each test and additional tests are conducted only if data generated indicate a need for more information. For example, if the ADMEK (absorption, distribution, metabolism, excretion, and kinetics) test indicates that the test substance is not absorbed, fewer or different studies would be conducted than if the material were absorbed.

Some tests are designed to address specific issues; e.g., reproductive effects, neurobehavioral effects, and carcinogenicity. The required tests and the specific test protocols should be developed on a case-by-case basis to address the unique issues presented by each functional ingredient. The tests that are generally needed include:

- Acute toxicity - develop a profile of acute toxicity in both sexes of several species;
- Comparative ADMEK - conducted in several species, human material in vitro used to identify the most appropriate species;
- Battery of genotoxicity tests - usually in vitro, followed by in vivo testing if indicated;
- Repeated dosing studies - 28 to 30 days in both sexes of rodent and/or dog; test for general and target organ toxicity, dose-related responses; NOAEL;
- Single dose studies in humans - test for acceptability/tolerance, ADMEK;
- Subchronic toxicity - 90 days in both sexes of rodent and/or dog; test for general and target organ toxicity, dose-related responses; NOAEL;
- Human repeated dosing - test for tolerability, toxicity;
- Reproductive and developmental toxicity - in rodent; test for reproductive and developmental (teratogenic) endpoints, NOAEL;
- Carcinogenicity- rat and/or mouse; and
- Allergenicity - consists of amino acid sequence analysis (similarity to known allergens), IgE binding in vitro (RAST and RAST inhibition, immunoblotting, histamine release from basophils), skin prick testing, antibody response to ingestion, and pepsin resistance.

Once the studies are completed, experts verify that the tests have been properly conducted. Dose-response relationships will be estimated along with the determination of a NOAEL for each study. Typically, the lowest NOAEL is usually selected as the basis for the ADI. The NOAEL is divided by an appropriate safety factor/uncertainty factor (e.g., based on the duration and/or sensitivity of the test, reliable human data), usually 10-1000. The ADI is then compared to the proposed intake levels to confirm the safety of the intended use.