ALTERNATIVE AND TRADITIONAL MODELS FOR SAFETY EVALUATION OF FOOD INGREDIENTS

December, 1998

Prepared for
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, DC 20204

under
FDA Contract No. 223-92-2185
Task Order #9
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edited by

Daniel J. Raiten, Ph.D.

LIFE SCIENCES RESEARCH OFFICE
American Society for Nutritional Sciences
9650 Rockville Pike
Bethesda, Maryland 20814
FOREWORD

The Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in relevant areas of biology and medicine.

This report was developed for the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA), in accordance with provisions of Task Order #9 of Contract No. 223-92-2185. The final report was prepared and edited by Daniel J. Raiten, Ph.D., Senior Staff Scientist/Project Leader. The report is based on discussions of, and materials evaluated by, an ad hoc Expert Panel convened by LSRO. The members of the Expert Panel were chosen for their qualifications, experience, and judgement with due considerations for balance and breadth in the appropriate professional disciplines. Members of the Expert Panel and others who assisted in the preparation of the report are identified in Chapter VI.

This study was initiated in September, 1995. In a notice in the Federal Register of March 4, 1996 the FDA announced that, as a component of Task Order #9, LSRO was inviting data, information, and views bearing on the topic under study (Food and Drug Administration, 1996). Accordingly, LSRO provided an opportunity for public oral presentations in an Open Meeting held on May 15, 1996, and for written submissions. One (1) individual made an oral presentation at the Open Meeting. Five (5) individuals and organizations have provided written submissions for consideration by the Expert Panel (FDA Docket No. 95N-0409). In addition to materials submitted to the LSRO Open File and FDA Dockets Management Branch, LSRO solicited opinion, comments, and responses to specific questions from 63 experts and interested parties in the field of safety evaluation of new foods and food substances. Of these 63 individuals and organizations, 13 originally responded. These responses were compiled into a publicly available tentative report that was intended to provide support for the deliberations of the Expert Panel and to, in part, frame the discussions at the Open Meeting. After the Open Meeting, the Expert Panel requested an additional solicitation from those individuals and organizations who had not originally responded; an additional four (4) responses were received. All organizations who contributed materials for this report are listed in Chapter VII. The LSRO wishes to express its appreciation to all organizations who have contributed materials for this study.

This review process was conducted in two phases. Phase I involved the recruitment and subsequent deliberations of a five-member Expert Panel and culminated in the release of the publicly available Background Document. Phase II began after the Open Meeting and involved the deliberations of a five-member Expert Panel. In the transition from Phase I to Phase II, one member of the original Panel resigned due to time constraints and was replaced by another scientist with expertise in food safety and toxicology. The Expert Panels met four times over the course of the study to assess the available data relevant to the task.

The report was drafted by the LSRO staff and includes the recommendations of the Expert Panel who reviewed each draft of the report and provided additional documentation and viewpoints for incorporation into the final report. However, the LSRO accepts full responsibility for the study conclusions and accuracy of the report. The listing of individuals in Chapter V does not imply that the individual Panel members specifically endorse all statements in the report. Further, the members of the Expert Panel requested that it be noted that due to the complexity of the issues involved and the limitations of time and resources, many aspects relevant to not only the questions raised in the Scope of Work but also to the Panel’s specific recommendations remain to be addressed.

The final report was reviewed and approved by the LSRO Scientific Advisory Committee. Upon completion of these review procedures, the report was approved and transmitted to FDA by the Executive Officer, American Society for Nutritional Sciences.
This LSRO report does not necessarily reflect the opinion of the individual members of the ad hoc Expert Panel or the members of the American Society for Nutritional Sciences.

12/30/98
Date

Michael Falk, Ph.D.
Director
Life Sciences Research Office
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EXECUTIVE SUMMARY

A. INTRODUCTION

In carrying out its responsibilities under the Food Additives Amendment (FAA), the FDA asked the Life Sciences Research Office (LSRO) for a report incorporating input from the scientific community on what is a "reasonable" amount and type of information needed for reaching a safety decision about new food ingredients, particularly those substances proposed for use at a high concentration in the diet. In short, the FDA sought a common sense approach supported by science that can be used to answer the core question facing those making decisions about new food ingredients.

Based on the deliberations of a five-member panel of experts in the fields of toxicology, regulatory toxicology, nutrition, food science, and experimental design/statistics, LSRO has prepared a comprehensive report that will provide the FDA with "recommendations on sets of circumstances under which the scientific community finds justification for the use of either alternative or traditional safety models to ensure the safety of food ingredients." In response to the Scope of Work outlined by the FDA, this comprehensive review includes discussions of: (1) circumstances prompting the need for new types of studies, (2) circumstances when traditional studies should not be required or should be modified or limited, and (3) the appropriate use of safety factors." Also included is a "description of the principles and criteria that would be used in the nontraditional or alternative situations and a ranking/weighting of these criteria and principles."

B. BACKGROUND

As a result of advances in technology and nutrition, new foods and food substances\(^1\) are becoming available that raise concerns about the appropriateness of the traditional approach to safety evaluation. The traditional approach as outlined in the FDA's "Toxological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food" (also known as the "Redbook"; FDA, 1982) relies on two key characteristics in making decisions about appropriate testing of new substances: exposure estimations and chemical structure. Among the changes contributing to the concern about the approach outlined in the Redbook are:

- The high exposure levels, particularly those greater than 0.1%\(^2\) of the diet, for some new products,
- The complexity of new foods and food substances\(^3\): Rather than single chemical entities many new foods and food substances are complexes consisting of numerous entities that make structure category assignment and subsequent testing difficult, and

\(^1\) The term substance is used in the definition of food additives, i.e., "...any substance the intended use of which results in..." As stated in 21CFR170.3, “the word substance in the definition of the term ‘food additive’ includes a food or food component consisting of one or more ingredients.” Because the definition of food additive includes reference to the term substance and a substance is subsequently defined as consisting of one or more food ingredients, the Expert Panel concluded that the term “new foods and food substances” are sufficiently inclusive to describe the range of materials to be covered by its recommendations.

\(^2\) This concentration was chosen as a reference point because substances present at concentrations >0.1% cannot be evaluated in animal trials using the 100:1 uncertainty factor approach (assumes that tests conducted using the substance at a dietary concentration >10% will lead to results that are not meaningful).

\(^3\) Complex substances are those that are chemically heterogeneous, and either do not pass the test of substantial equivalence or provide an obvious frame of reference for such comparisons as described in the structure categorization process outlined in Redbook (FDA, 1982).
• The potential, due to either the nature of the source material or the process used to produce the new substance, for producing effects in humans that are not reproducible and/or detectable in animals, thereby requiring some process by which these effects can be predicted and subsequently tested in humans or confirmed with some appropriate surrogate marker in a relevant animal model.

Each of these factors necessitates a flexibility in approaches to safety evaluation. Some of the other limitations of the traditional approach are the emphasis on toxicology as defined as measurable cellular damage, limited use of functional outcomes in metabolism and physiology, the over-reliance on and relevance of animal models, limited use of human clinical trials, and the applicability of traditional uncertainty factors.

A seminal issue precipitating the increased attention to the need for alternative approaches is the level of exposure that are projected for many of the new substances that have and will be introduced into the food supply. The high level of exposure often projected for these new materials, frequently greater than 0.1% of the diet, necessitates a reevaluation of how potential hazards can be identified and how safe levels of consumption by humans can be determined. Examples of the types of problems that might occur as a consequence of these high exposure levels include:

• Standard toxicological feeding trials involving administration of whole foods (as in the case of a genetically modified variety of fruit or vegetable) or substances that, when consumed, might constitute a significant portion of daily dietary intake (such as a fat substitute) often produce adverse effects simply as a result of dietary imbalance rather than an inherent toxicity per se.

• Identification and application of uncertainty factors for the derivation of the acceptable daily intake (ADI)\(^4\) pose new problems. In the case of substances with a simple chemical structure that are consumed at relatively low concentrations in the diet, animal studies can be designed with confidence that the maximum doses tested will permit the application of standard uncertainty factors, e.g., 100:1, when the substance is used commercially. This is usually not the case with substances present in the diet at high concentrations, i.e., greater than 0.1% of the diet.

C. CONCLUSIONS AND RECOMMENDATIONS

Preceded by an overview of the legislative history of FDA’s mandate in the area of food safety review and regulation, and positions of other authoritative organizations, the report includes a description of the principles and criteria that undergird the recommendations of the Expert Panel. The Expert Panel described the safety evaluation of new foods and food substances as a dialectical process involving the generation of an estimate of risk based on scientific principles and the safety decision made in the context of society’s perceived needs. In keeping with the Scope of Work, the focus of the Panel’s recommendations was on the scientific component of safety evaluation.

Chapter III contains an expansive discussion of a set of principles intended to address issues raised by both traditional food additives and new foods and food substances distinguished by their complexity, high exposure estimates, and/or the novelty of their source materials or production process. Among the concepts presented is the description of the universe of materials to be covered by the Panel’s recommendation as ranging from traditional type food additives, all

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\(^4\) The Expert Panel concluded that because the goal of the risk assessment is a reflection of risk from both acute and chronic exposure, with an emphasis on the latter, the term acceptable chronic intake (ACI) would be used rather than the traditional ADI.
the way to genetically modified foods. Along with a discussion of the justification for the need for an alternative approach, other relevant issues covered included the concept of substantial equivalence and the Panel’s view of the scientific component of the safety evaluation as a risk assessment. The latter discussion includes a presentation of the Panel’s definition of what constitutes an adverse effect. An additional element covered in Chapter III is the question of what constitutes a reasonable standard for comparison or “control” to establish whether an effect occurs and is harmful.

The goal of the Panel was not to abolish the traditional approach to safety evaluation of new foods and food substances, but rather to adapt it and utilize appropriate elements (or add new ones wherever warranted) for the evaluation of these materials. In recognition of the strengths of the "traditional approach," the Panel acknowledged that the new model is similar to the principles applied in the Redbook, but also differs in emphasis and application. The Panel emphasized that irrespective of the approach used, either traditional or nontraditional, the selection of appropriate tests must be done on a case-by-case basis with due consideration of exposure estimates, source material, complexity, and process.

The Expert Panel recognized that its task was to provide advice on the type and amount of scientific data required to make a decision about the risk associated with the proposed use of new foods and food substances, in particular, those that require testing that might be classified as nontraditional. The Panel concluded that the scientific standards required to make a decision about the risk associated with the proposed use of a given new substance should be the same irrespective of the regulatory classification, e.g., a food additive, GRAS, or new food. The Expert Panel therefore offered the following tenets with regard to the evaluation of new foods and food substances:

- To establish recommendations for the types of testing required for the risk assessment of new foods and food substances, it is essential that the types of effects that constitute harm be specified as accurately as possible.

- The nature and extent of the testing conducted for a new substance must be commensurate with the predicted risks to humans under proposed conditions of use.

- Testing procedures selected for new foods and dietary components that because of their nature or proposed conditions of use, i.e., those that will appear at high concentrations in human diets, obviate or limit the traditional use of animal studies must include an increased emphasis on clinical trials in humans and decreased emphasis on traditional toxicological procedures.

- For those substances of simple chemical composition derived from conventional sources by conventional methods and occurring at low concentrations in food e.g., < 0.1%, the approach recommended by the Expert Panel is consistent with principles outlined in the Redbook; however, details of implementation may differ in some instances.

The proposed model for reaching decisions about testing of new foods and food substances is detailed in Chapter IV. To encompass all of the potential substances to be covered in the report, the Expert Panel offered a procedure to determine appropriate testing strategies that incorporates elements of the traditional approach and additional elements necessitated by the nature of these new substances. The Panel emphasized that irrespective of the choice, traditional animal toxicology tests or the combination of animal testing along with increased emphasis on clinical trials in humans, the scientific component of safety evaluation of new foods and food substances is a risk assessment, and as such used the components outlined by the NRC (1982, 1994) in presenting its model. Each element of the risk assessment, i.e., exposure estimation, hazard identification, dose-response assessment, and risk characterization, is covered in detail with specific recommendations for implementation. The process includes a new categorization scheme that is an evolution of the approach used to determine concern levels presented in the Redbook (FDA, 1982) and incorporates those elements that have contributed to the need to reevaluate this traditional approach, i.e., complexity, source materials, productions process, and high estimated exposure levels.
The Expert Panel understood that because of the complexity of the subject matter and limitations in time and resources, its presentation would be limited primarily to a delineation of the concepts deemed essential to the implementation of its recommendations. The Panel also acknowledged the efforts of a number of organizations and agencies both domestically and internationally who have presented informative and useful descriptions of many of the technical issues pertaining to the safety evaluation of new foods and food substances. As outlined in Chapter II of this report, these authoritative reports outlined many of the technical issues associated with risk assessment of these new materials. However, the Expert Panel identified several key technical issues that require further examination:

- Estimation and effective incorporation of uncertainty factors into the risk assessment and risk management process: The Expert Panel has noted throughout this report that a consequence of the advent of the new types of foods and food substances covered in its recommendations is the inability to apply traditional safety factors, e.g., 100:1, in the conduct of animal toxicology tests. The Expert Panel strongly endorsed an expanded discussion of how to identify and quantify those elements that contribute to the inherent variability found throughout the various stages of the risk assessment, i.e., exposure estimation, hazard identification, and quantification of the risk estimate. Many of these issues were addressed broadly in the JECFA report “Application of Risk Analysis to Food Standards Issues” (Joint FAO/WHO, 1995). The Panel urged an expansion of this discussion.

- A detailed description of the process for the generation of a quantitative measure of risk: the ADI has been the traditional endpoint in the safety evaluation of new foods and food substances. The Expert Panel adopted the term acceptable chronic intake (ADI) as being more reflective of the goal of the risk assessment. However, a more detailed discussion will be needed of how that estimate is derived. In particular, specific attention must be paid to the process for assessing potential chronic effects.

As noted throughout this report the potentially high levels of exposure of some new foods and food substances obviate the traditional approach to the use of animal studies and necessitate the increased use of clinical trials in humans. However, a limitation of human trials in the premarket phase of the risk assessment is the difficulty in conducting long-term studies. Consequently, chronic animal studies will continue to play an important role in this part of the assessment process. The choice of appropriate markers/endpoints, and the nature and dose of the substances to be evaluated must be based on the best available science and an effective dialogue between the petitioner and the scientific staff of the FDA or appropriate regulatory agency.

In addition, an expanded coverage will be needed for how a quantitative risk estimate for the general population and for specific “at risk” groups will be generated and subsequently implemented in the risk management phase of the evaluative process.

- Case-study applications of the alternative models: the Expert Panel strongly encourages the application of the proposed model to hypothetical cases of new foods and food substances in order to work out the details, e.g., estimation of appropriate doses for control substances to be used in some of the hypothesis testing protocols outlined in Table 4-5, of the process prior to its implementation.

Recommendations about which tests to use to support a petition for a new food or food substance have historically been, and will continue to be, made by the highly qualified scientists of the FDA with an appreciation for the evolving state of the science and resource availability. Irrespective of the choice and methods used, the end result of this process must be the generation of a science-based reliable and valid estimate of risk that can be used to make a safety decision that will meet the standard of a “reasonable certainty of no harm.”
I. INTRODUCTION

A. LEGISLATIVE HISTORY

The legislative history of regulation of the food supply began with the passage of the Pure Food and Drug Act of 1906 (Pure Food and Drugs Act. 1906. 34 U.S. Stat. at Large 768). The 1906 Act was subsequently replaced by the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) which expanded the authority of the Food and Drug Administration (FDA) as the proprietary agency responsible for the safety of the food supply (Federal Food Drug and Cosmetic Act. 1938, PL 75-717 Stat 1040 as amended USC 301-392 [21982]).

In section 201 of the FDCA, food was defined as "(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. (FD&C Section 201f)." Under section 401 of the FDCA, the FDA is given authority to promulgate "regulations fixing and establishing for any food, under its common or usual name so as practicable, a reasonable definition and standard of identity, a reasonable standard of quality, and/or reasonable standards of fill of container." According to Kessler (1995), the FDCA "authorized the FDA to 'create standards of identity' specifying the ingredient composition of cheeses, frozen desserts, and canned fruits and vegetables as well as the nutrient fortification of cereals and breads, milk, and macaroni and noodle products." In addition, the 1938 Act "required that claims of special dietary properties be based on sound science and that label information be truthful and not misleading" (Kessler, 1995).

With regard to food safety, the FDCA presupposed two assumptions: first, food is inherently safe, and second, the burden for proving otherwise rests with the FDA. Section 402 of the FDCA described those situations when a food was to be considered "adulterated." The standard for harm in this case was that foods are considered safe unless data exist to indicate that they are "ordinarily injurious to health" when consumed. However, knowledge of the toxicity of inherent components (for example, solanine in potatoes) would not be sufficient to warrant action by the FDA unless it could be proven that "the quantity of such components may ordinarily render the food to be injurious to health."

Subsequent to passage of the FDCA, addition of non-inherent substances to food became increasingly common and was accompanied by an increase in public concern about food safety. This concern led to the passage of the 1958 Food Additives Amendment (FAA) to the Federal Food, Drug, and Cosmetics Act (PL 85-929; Federal Food, Drug, and Cosmetic Act. 1958. Food Additives Amendment Sect. 409. 348a). As noted in the preamble, this Act was created "To protect the public health by amending the Federal Food, Drug, and Cosmetic Act to prohibit the use in food of additives which have not been adequately tested to establish their safety."

Paramount among the provisions of this amendment was that the burden for proving safety of new food additives was placed on manufacturers or sponsors through a pre-market approval system. In effect, with regard to food additives, the role of the FDA was changed from "police officer" to "gatekeeper" (Merrill, 1997: presentation at second meeting of the Expert Panel). The legislation makes it clear that the concept of safety intended by the FAA "involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of the additive. It does not – and cannot – require proof beyond any possible doubt that no harm will result under any conceivable circumstance." (U.S. Congress, 1958). Under the FAA, relevant factors to be considered include probable consumption of the additive and any substance formed because of the use of the additive, cumulative effects of the additive and pharmacologically related substances in the diet, and safety factors that qualified experts generally recognize as appropriate for the use of animal experimental data (the Act and 21 CFR 170.3[1]).

The 1958 amendment provided parameters and definitions that apply to different situations that the FDA faces in making decisions on food safety. The following definitions provide useful background for the discussion of the safety evaluation of new food substances.
Food additives: The 1958 FAA stated: "The term food additive means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the condition of its intended use; except that such a term does not include –

1. a pesticide chemical in or on a raw agricultural commodity; or
2. a pesticide chemical to the extent that it is intended for use or is used in the production, storage, or transportation of any raw agricultural commodity; or
3. a color additive; or
4. any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph pursuant to this act, the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907 (34 Stat. 1206, as amended and extended (21 U.S.C. 71 and the following))."

Generally Recognized as Safe (GRAS) substances: GRAS status is based "only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. In the first case, GRAS status "based on scientific procedure shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient." (21 CFR 170.30, 1994)

In the second case, GRAS status based on common use in food prior to January 1, 1958, safety "may be determined without the quantity or quality of scientific procedures required for approval of a food additive regulation." The Food Additives Amendment of the Act makes it clear that "an ingredient not in common use in food prior to January 1, 1958, may achieve general recognition of safety only through scientific procedures."

Substances: The term substance is used in the definition of food additives, i.e., "...any substance the intended use of which results in..." As stated in 21CFR170.3, "the word substance in the definition of the term 'food additive' includes a food or food component consisting of one or more ingredient."

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1 The recently passed PL 104-170, known as the "Food Quality Protection Act of 1996" (FQPA) has amended the FDCA to include not only pesticides and residues on raw foods but those pesticides and residues found in processed foods. Specifically, FQPA defines a pesticide chemical as "any substance that is a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act [FIFRA], including all active and inert ingredients of such pesticide." (H.R. 1627, Title IV, Section 402[1], 1996) Further, FQPA defines pesticide chemical residual as "a residue in or on a raw agricultural commodity or processed food of (A) a pesticide chemical or (B) any other added substance that is present in or on the commodity or food primarily as a result of the metabolism or other degradation of a pesticide." (H.R. 1627, Title IV, Section 402[2], 1996).

2 21CFR170.3 does not include a definition of a food ingredient. Because the definition of a food additive includes reference to the term substance and a substance is subsequently defined as consisting of one or more food ingredients, the Expert Panel concluded that the terms "new foods and food substances" are sufficiently inclusive to describe the range of materials to be covered by its recommendations.
Although the FDCA and its subsequent revisions contained provisions authorizing the FDA to insure the safety and quality of the food supply, e.g., providing regulatory protection against the addition of unsafe substances, there are situations that have arisen with the advent of new production techniques that warrant an appraisal of how the FDA approaches the safety evaluation of food. The underlying premise for the Panel's recommendations in this report is that circumstances that have evolved through advancements in technology and nutrition that necessitate a reevaluation, and perhaps development of alternative approaches to, the safety evaluation of new foods and food substances.

B. SAFETY EVALUATION

1. The "Traditional Approach": The Redbook

Safety for any of the possible categories of new food s and food substances "means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use." (21 CFR 170.3(i)) Because it is impossible to prove absolute safety, FDA must determine what is a reasonable quantity of what types of information to require to support a decision that a new substance to be added to the food supply is safe.

As mandated by the FAA, the burden for proving safety of new food additives lies with the manufacturers or sponsors through a pre-market approval system. In the document "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food" (commonly referred to as the "Redbook"), the FDA established guidelines for toxicological testing to be used by those petitioning for approval of a new food additive (FDA, 1982).

The Redbook has two specific stated purposes:

"First, to delineate FDA's most up-to-date scientific criteria for establishing the safety of direct food additives and color additives used in food, and, second, to establish a process for monitoring that safety."

Clearly, these goals define a dynamic document that is designed to provide guidance to petitioners through an evolving presentation of recommendations. In particular, the second purpose suggests a process that is continuous and includes an active postmarket component.

As outlined in the Redbook (FDA, 1982), the approach to the determination of safety must include knowledge of three core components: chemical identity, exposure estimates, and the application of a safety factor, generally accepted as 100-to-1 (100:1) after derivation of the no observable adverse effect level (NOAEL) in appropriate toxicological testing paradigms. Specifically, 21 CFR 170.3 (i)(1-3) states that the determination of safety must include consideration of the following factors:

- Probable consumption of the substance and of any substance formed in or on food because of its use;
- the cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet; and
- safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

In application, the endpoint of the process of safety evaluation is the generation of an estimate of the acceptable daily intake (ADI) for a direct food additive or color additive used in food. As stated in the Redbook, "the ADI is typically based on the dose level of the additive in animal studies that was shown to cause no observable adverse effect (NOAEL), multiplied by an appropriate safety factor (often 1/100). Chronic ingestion of the additive at the ADI is considered consistent with a reasonable certainty of no harm."
Generally, in the extrapolation of data from animal studies to humans, a factor, most often referred to as a "safety factor," has been generated and used by the FDA to make safety decisions. According to 21 CFR 170.22, "...Except where evidence is submitted which justifies use of a different safety factor, a safety factor in applying animal experimentation data to man of 100 to 1 will be used..."

In their landmark essay on the need for the 100:1 uncertainty factor, Lehman & Fitzhugh (1954), FDA scientists who helped to establish this regulatory paradigm stated that "the term '100-fold margin of safety' signifies that the chemical additive should not occur in the total human diet in a quantity greater than 1/100 of the amount that is a minimum safe dosage in long-term animal experiments."

According to Lehman & Fitzhugh (1954), the justification of the 100:1 uncertainty factor was based on the following five factors:

- uncertainty of direct extrapolation from animal data;
- variations between animal species;
- variation within strains of animal species;
- the difference between a controlled animal experiment using a homogeneous group of animals and conditions of exposure to the heterogeneous population of humans who may be experiencing varying degrees and types of physiological stress, e.g., heat or cold, sickness, and dietary insufficiency; and
- the potential additive effects of new ingredients on top of those already in the food supply.

The two prime considerations providing the basis for the 100:1 factor are uncertainty relative to the extrapolation of animal data to humans and the variability among humans. The underlying assumptions justifying the use of uncertainty factors are that there may be differences in the susceptibility to the effects of a given substance between humans and experimental animals and there are differences in susceptibility among humans. However, these variabilities are not necessarily constant as would be inferred from the codification of the 100:1 factor. As noted by the National Research Council (NRC) in its 1994 report on risk assessment, while the assumptions upon which the 100:1 factor is based are "plausible,...the magnitude of interspecies and intraspecies differences for every chemical and toxic end point are not often known." (NRC, 1994, p. 63). Consequently, while the application of the 100:1 factor has been useful for most direct food additives because they are relatively nontoxic and typically are used in low concentrations in food, in practice, over the years there have been numerous circumstances (e.g., evaluations of individual amino acids and other nutrients) where the 100:1 factor was not applicable and other factors were employed.

At the core of the recommendations set forth in the Redbook is the concept of concern levels (CL). In practice, the FDA has historically based its safety evaluation on estimations of exposure which, along with knowledge about chemical structure, dictate that amount of toxicological or other biologic safety data required to reach a decision. For a given food additive, the process, as outlined in the Redbook (FDA, 1982), involves the computation of a CL. Table 1 summarizes the criteria for assigning CL to a given food additive and the tests recommended at each level.

The Redbook also suggested that although not required for any specific CL, absorption, distribution, metabolism, and elimination (A,D,M,E) studies should be included in the data submitted for any test substance, particularly prior to the conduct of toxicity studies longer than 90 days in duration. These types of tests serve to aid in interpretation of other toxicological tests, extrapolation of animal tests to humans, and are useful in the establishment of appropriate dose levels for chronic toxicity and carcinogenicity tests.

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3 While recognizing that the term, "safety factor" is part of the FDA's regulatory vernacular, the Expert Panel regards "uncertainty factor" as a more appropriate term as it embodies the uncertainty associated with extrapolating data from animal studies to humans, the variability inherent in the population of humans exposed to a new ingredient, and a true, but largely undetermined, margin of safety. Moreover, the use of the term uncertainty factor is consistent with recent attempts (consequent to the passage of FQPA) to harmonize the approaches used in safety evaluation of food by the FDA with safety evaluations of other substances by groups such as the Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA) (NRC, 1994).
In addition to recommendations about the core tests indicated under each CL, the Redbook, included "a framework" for deciding what additional tests might be needed based on "decision elements." Two types of decision elements were identified:

- **Selection elements**

  These elements provide, "in a stepwise fashion," the criteria for the selection of the most appropriate test(s) to be used to follow up concerns raised by the appearance of adverse effects in the available data. Essentially, selection elements provide the basis for the determination of what additional tests might be needed beyond those delineated for a given CL. If the core tests indicate a safety concern, the selection elements will help determine which test would be required to resolve the safety decision. Selection elements would be used in any case where a safety decision is required for a food ingredient and would apply not only to pre-market safety decisions but also in cases where additional data either increased exposure estimates or new toxicological data become available.

- **Ranking elements**

  In the case where information about a previously approved additive indicates a potential change in the safety estimate, e.g., changes in exposure estimates, ranking elements "determine a sequence for the conduct of selected studies for the development of new information." Because all additives do not engender the same level of concern, a process was needed that could be universally applied to all additives and would allow the FDA to prioritize those additives that required greater attention and resources.

  The conceptual justification of ranking elements is to "allow the FDA to assess relative concerns for additives so that it may devote more of its resources to those additives that are of highest potential public health concern." While selection elements are focused on additional toxicological testing requirements, ranking elements allow the FDA to determine testing priorities within a broader context that includes considerations of such factors as "economic limitations or administrative or other constraints."

2. **Redbook II**

The revised draft of the Redbook ("Redbook II"; FDA, 1993) proposes to expand the types of recommended tests to include other types of toxicology testing, e.g., metabolism and pharmacokinetics, neurotoxicology, and immunotoxicology. Redbook II, first made publically available for comment in March of 1993 (FDA, 1993) has not as yet been released in final form.

In revising the original Redbook, it was decided to focus only on those issues pertaining to data necessary for the initial review of a new petition rather than include discussions of both pre- and post-decision data requirements. Although not included in the text, conceptually, the decision elements remain an integral part of the review process.

Other changes presented in Redbook II include:

- changes in the criteria for determination of CL, including revision in estimation of exposure and structure categorization;

- addition of tests to each CL (see Table 1);
<table>
<thead>
<tr>
<th>Concern Level</th>
<th>Structure Category A</th>
<th>Structure Category B</th>
<th>Structure Category C</th>
<th>Recommended Tests</th>
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<tbody>
<tr>
<td>I</td>
<td>&lt;0.05 ppm in the total diet (&lt;0.0012 mg/kg/d)</td>
<td>&lt;0.025 ppm in the total diet (&lt;0.00063 mg/kg/d)</td>
<td>&lt;0.0125 ppm in the total diet (&lt;0.00031 mg/kg/d)</td>
<td>• short-term feeding study (≥28 d) in a rodent species; • short-term carcinogenicity tests designed to determine priority for conduct of lifetime carcinogenicity bioassays (these tests may also be used to evaluate results of such bioassays when warranted)</td>
</tr>
<tr>
<td>II</td>
<td>≥0.05 ppm in the total diet (≥0.0012 mg/kg/d)</td>
<td>≥0.025 ppm in the total diet (≥0.00063 mg/kg/d)</td>
<td>≥0.0125 ppm in the total diet (≥0.00031 mg/kg/d)</td>
<td>• subchronic feeding study (≥90d) in a rodent and nonrodent species; • multigeneration reproduction study (minimum of two generations with a teratology phase) in a rodent species; • short-term carcinogenicity tests</td>
</tr>
<tr>
<td>III</td>
<td>≥1.0 ppm in the total diet (≥0.25 mg/kg/d)</td>
<td>≥0.5 ppm in the total diet (≥0.0125 mg/kg/d)</td>
<td>≥0.25 ppm in the total diet (≥0.0063 mg/kg/d)</td>
<td>• carcinogenicity tests in two rodent species; • a chronic feeding study ≥ 1 y in a nonrodent species; • multigeneration reproduction study (minimum of two generations) with a teratology phase in a rodent species; • short-term tests for carcinogenic potential</td>
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</table>

Additions in Redbook II include short-term screening tests for neurotoxicity and immunotoxicity in rodents. Additions in Redbook II include metabolism and pharmacokinetic studies; neurotoxicity and immunotoxicity tests added to the subchronic toxicity and reproduction with teratology tests in rodent and nonrodent species.

Additions in Redbook II same as for Concern Level II. Additionally, a subchronic feeding study with rodents to be completed prior to carcinogenicity bioassays.

Adapted from Kotsonis et al. (1996) and FDA (1982, 1993)
• recommendations for changes in toxicity testing guidelines. In part, these changes reflect not only advances in technology and understanding of physiology/pharmacology, but also an increased awareness and sensitivity to issues involving the ethical use and treatment of animals for scientific research;

• an increased emphasis on the importance of neurotoxicology and immunotoxicology testing;

• an increased emphasis on human studies. While the FDA has not historically required data from human clinical studies to be included in petitions, it encourages petitioners to include such data. In response to the potential increase in the availability of such data, Redbook II offers guidelines for the conduct of such studies.

• to be responsive to potential issues that may arise as the result of the introduction of new processes in food technology leading to new food and food substances that do not fit the "traditional model," Redbook II includes suggestions about special tests or approaches to testing that might be useful in the assessment of several categories of new food substances. These categories and examples include additives intended for use at high levels of exposure (macro-additives), bioengineered additives, additives that are enzymes, and microbiologically derived additives.

Consistent with the historic goal of creating and promulgating a document that is dynamic and evolving in response to changes in the food additive environment, Redbook II has not been finalized as the FDA continues to revise and redefine its concept and content in response to public input.

3. Post-approval process

Although there are many differences in the presentation of materials between the two versions, one prominent component discussed in the original Redbook, the decision elements (i.e., selection and ranking elements), which ultimately became known as the Priority Based Assessment of Food Additives (PAFA) system, has been removed from the Redbook II. PAFA is essentially a database containing all available toxicological information on regulated food ingredients. Because of resource limitations, the FDA no longer performs a cyclic review of food additives. It does, however, continue to collect relevant data to be included in the PAFA database. To decide on the order of the post-approval review process, food additives are assigned priority scores which are derived mathematically from an estimate of the lowest observed effect level (LOEL) and exposure estimates.

Consistent with the goal of having a safety evaluation process that is dynamic and evolving in response to advances in technology, part of the impetus for Redbook II was the realization that the "traditional approach" to food safety evaluation was not inclusive enough to cover these new types of food ingredients. While the Redbook is a useful tool, it is not codified as the definitive standard or criterion for the establishment of safety. Moreover, it has become evident that the advent of emerging technologies such as genetic engineering of traditional foods and the production of macronutrient substitutes are examples of situations where a different or additional approach to safety assessment is needed. While the FDA has rendered decisions on foods derived from such new technologies on a case-by-case basis, it has become clear that a need exists for principles and criteria that the scientific community can generally apply to these situations.

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4 As stated in the Foreword of Redbook II (FDA, 1993), the rationale for omitting a presentation of the PAFA elements was that "it is beyond the scope of this document to provide a comprehensive list of all types of information in PAFA, or to provide a complete description of the procedures now used to evaluate data prior to inclusion in the [PAFA] database." The drafters of Redbook II go on to say that the FDA "will continue to make information about PAFA available to the public upon request..."
C. OBJECTIVE AND SCOPE OF THE STUDY

In carrying out its responsibilities under the FAA, the FDA asked the Life Sciences Research Office (LSRO) for a report incorporating input from the scientific community on what is a "reasonable" amount and type of information needed for reaching a safety decision about new food ingredients, particularly those substances proposed for use at a high concentration in the diet. In short, the FDA sought a common-sense approach supported by science that can be used to answer the core question facing those making decisions about new food ingredients.

Specifically, LSRO was asked to prepare a comprehensive report for the Center for Food Safety and Applied Nutrition (CFSAN) that will provide FDA with "recommendations on sets of circumstances under which the scientific community finds justification for the use of either alternative or traditional safety models to ensure the safety of food ingredients." This comprehensive review should include: "(1) circumstances prompting the need for new types of studies, (2) circumstances when traditional studies should not be required or should be modified or limited, and (3) the appropriate use of safety factors." The FDA also asked for a "description of the principles and criteria that would be used in the nontraditional or alternative situations and a ranking/weighting of these criteria and principles."

In framing the discussions for the report, the FDA suggested that the following questions be considered. As stated in the contract Scope of Work, "These questions were not intended as a statement of specific tasks. They were intended to be illustrative and to be used as a basis to stimulate thought regarding the determination of the safe use of food ingredients.

1. In what cases are animal feeding studies not necessary to ensure safety? As examples, do such studies need to be conducted for ingredients that also occur naturally in foods at similar or higher concentrations? Is it reasonable and necessary to test food-like substances for toxicity and nutritional influences, recognizing the potential for confounding results? If so, how?

2. To what extent can chemical and structural similarity to food ingredients known to be safe obviate the need for animal or human testing?

3. What criteria should be used to determine when a treatment-related effect (including effects from nutritional imbalance or interference) is an adverse effect?

4. Are there criteria that can be used to determine whether an adverse effect observed in a study is relevant to human safety, as opposed to an effect that is dependent on study design and has no relevance to safety under actual use conditions?

5. Under what circumstances should clinical studies in humans supplement, or replace, studies in laboratory animals? Which parameters should be measured and what study duration is necessary?

6. Is there an agreed-upon basis for determining the maximum level of an additive in a test diet, above which a study should be presumed unacceptable?

7. Can postmarketing surveillance (both monitoring of use and monitoring of adverse reactions reports by consumers and physicians) be used to ensure safety? For example, can it be used without compromising safety to verify exposure estimates or to eliminate the need for specific data prior to marketing, thus reducing the need to use worst case assumptions in a safety evaluation? If so, how could this be accomplished?"

D. STUDY APPROACH

This study was divided into two phases. Phase I involved the recruitment of a five-member Expert Panel. The Expert Panel understood that although it would attempt to reflect the opinions and concerns of the scientific community about
safety evaluation of food ingredients, it did not necessarily represent that community. In an attempt to gain as much insight as possible about the views and concerns from a cross section of the scientific and advocacy communities, the LSRO solicited comments from 63 members of the community of scientists and other parties and organizations interested in the safety evaluation of food ingredients. LSRO originally received 13 responses to its letter soliciting opinions and suggestions from the scientific community on the question of the safety evaluation of new foods and food substances.

The nature of the solicitation was a request to respond to the following questions about the safety evaluation of new foods and food substances.

1. Strengths and weaknesses of the current scientific aspects of food safety evaluation.

2. Proposed changes in the criteria for safety evaluation (including methods and scientific disciplines required to be included in the establishment of new approaches).

3. Rationale and circumstances which require changes in the safety evaluation of a food ingredient, including examples of new technologies or products that the responders envision will require a new approach.

A Background Document was prepared that represented the compilation of comments received in response to the Phase I solicitation. This document was intended to provide background and perspective to the Phase I Expert Panel. It did not reflect the views or conclusions of the Phase I Expert Panel and was not a draft of the final report prepared for the FDA.

Following the release of the Background Document, a Public Meeting was held to obtain input from members of the general community who wished to comment on the topics to be covered in this study. Oral comments were presented by one organization. Individuals contributing written materials to this report are listed in Chapter VII. Both the project and the Public Meeting were announced in the Federal Register (FDA, 1996).

At the behest of the Phase I Expert Panel an additional scientist was enlisted with expertise deemed necessary to address the issues identified in the Scope of Work. In addition, one of the original members of the Phase I Panel retired due to time constraints. Consequently, the Phase II Expert Panel consisted of the five members listed in Chapter V. In addition to reviewing the literature and available data, the Expert Panel requested a further solicitation of comments from those individuals who had not responded to the initial Phase I solicitation. An additional four comments were received. Comments received from the original solicitation and the additional comments received in the subsequent solicitation have been reproduced verbatim in Appendix A.
II. THE NEED FOR ALTERNATIVE APPROACHES

A. UNDERSTANDING THE PROBLEM

As a result of advances in technology and nutrition, new foods and food substances are becoming available that raise concerns about the appropriateness of the traditional approach to safety evaluation. The traditional approach as outlined in the FDA’s "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food" (also known as the "Redbook") relies on two key characteristics in making decisions about appropriate testing of new substances: exposure estimations and chemical structure. Among the changes contributing to the concern about the approach outlined in the Redbook are:

* The high exposure levels, particularly those greater than 0.1% of the diet, for some new products;

* the complexity of new foods and food substances. Rather than single chemical entities many new foods and food substances are complexes consisting of numerous entities that make structure category assignment and subsequent testing difficult; and

* the potential, due either to the nature of the source material or to the process used to produce the new substance, for producing effects in humans that are not reproducible and/or detectable in animals, thereby requiring some process by which these effects can be predicted and subsequently tested in humans or confirmed with some appropriate surrogate marker in a relevant animal model.

Each of these factors necessitates a flexibility in approaches to safety evaluation. Some of the other limitations of the traditional approach are the emphasis on toxicology as defined as measurable cellular damage, limited use of functional outcomes in metabolism and physiology, the over-reliance on and relevance of animal models, limited use of human clinical trials, and the applicability of traditional uncertainty factors.

A seminal issue precipitating the increased attention to the need for alternative approaches is the projected level of exposure for many of the new substances that have and/or will be introduced into the food supply. The level of exposure often projected for these new materials, frequently greater than 0.1% of the diet, necessitates a re-evaluation of how potential hazards can be identified and how safe levels of consumption by humans can be determined. Examples of the types of problems that might occur as a consequence of these high exposure levels include:

* Standard toxicological feeding trials involving administration of whole foods (as in the case of a bioengineered variety of fruit or vegetable) or substances that, when consumed, might constitute a significant portion of daily dietary intake (such as a fat substitute) often produce adverse effects as a result of dietary imbalance rather than an inherent toxicity per se.

* Identification and application of safety factors for the derivation of the acceptable daily intake (ADI) pose new problems. In the case of substances with a simple chemical structure that are consumed at relatively low concentrations of the diet, animal studies can be designed with confidence that the maximum doses tested will permit the application of standard safety factors when the substance is used commercially. This is usually not the case with substances present in the diet at high concentrations.

B. POSITIONS OF OTHER AUTHORITATIVE AGENCIES REGARDING SAFETY EVALUATION OF NEW FOODS AND FOOD SUBSTANCES

In order to provide context and perspective, the Expert Panel considered the positions of authoritative organizations and individuals, both domestic and international, with regard to the process involved in the evaluation of new foods and food substances. Summarized in Tables 2-1 and 2-2 are the positions of various authoritative organizations with
Table 2-1. Positions of other authoritative agencies on the safety evaluation of new foods and food substances.

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| (U.K.) Committee on Medical Aspects of Food Policy, Panel on Novel Foods (PNF) (1993) | The PNF was charged with providing advice as to the “nutritional implications and consequences of including Olestra in the diet,” and recommending “how best to assess the implications for the national diet of recent and possible future developments in novel foods and processes.” Consequently, the report was focused on:  
- nutritional issues associated with the evaluation of novel foods and processes in U.K. and E.C.;  
- discussions of several specific examples of novel foods including Olestra,  
- recommendations on methods to assess nutritional aspects of advances in food technology;  
The report also contained a brief review of U.K. and E.C clearance processes and a listing of principles to be used in the nutritional assessment of novel foods.  
The PNF viewed novel foods in the context of evolving science on the relationship between diet and health and considered that “novel foods have the potential to influence dietary habits in ways which can be either beneficial, leading to decreased risks for chronic or other diseases, or adverse, leading to increased risks for the populations consuming them. The Panel therefore concluded that in assessing the nutritional implications of novel foods or food processes, the potential impact on public health should form a major and integral part of the Panel’s Terms of Reference.” | All foods including novel foods are currently controlled in the UK under the provisions of the food Safety Act 1990. Pre-market clearance of novel foods and food processes is not part of the Act and is voluntary, manufacturers are therefore free to market their products subject only to the requirements of the Act but are encouraged to submit for clearance. Clearance of a food or food process does not constitute formal approval; rather it is a confirmation that on the evidence presented, Ministers see no food safety reason why the food should not be legally marketed in the UK.”  
The PNF supports the need for scientific progress in novel foods and processes, will provide guidance on nutritional assessment and recommendations on acceptability of specific novel foods when requested. |
<p>| Advisory Committee on the Assessment of Novel Foods and Processes (ACNFP, 1991) Guidelines on the Assessment of Novel Foods and Processes | Included working definitions of novel foods and food processes, and outlined a decision tree for determining appropriate testing for a new food or food substances. The criteria for testing were the source, process and use of the new substance with testing ranging from only nutritional testing requirements for materials with only a novel use to more complex testing requirements for genetically modified live organisms such a yogurt cultures. | The decision tree included some consideration for level of exposure with regard to toxicological testing. The ACNFP noted that “the traditional method of assessing the safety of a food additive, i.e., allowing a one hundred-fold margin between the maximum amount of the additive likely to be consumed in the human diet and the maximum amount which has no toxic effect when fed to animals, clearly cannot be applied to a food which would constitute more than one per cent of the human diet.” |</p>
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<td>ACNFP (1994) (United Kingdom)</td>
<td>The focus of this revision of the 1991 Guidelines was on assessment of novel foods “produced other than by traditional plant breeding.” The document contains a further refinement of the definition of novel food to include “... the organism itself, be it a micro-organism, plant, or animals (or part thereof), or it may be a product derived from such an organism. A novel food may be equivalent to an existing product but be produced by an extensively modified or entirely new process, for example, a food component previously extracted from plants now being produced from a recombinant micro-organism. Existing foods may also be subjected to novel processes.” The report includes a revision of the decision tree presented in 1991, and adds “fifteen new structured schemes each of which further refines/amplifies its corresponding information requirement.” The distinguishing features of this revision are that the “new tree distinguishes between: a single cell product produced by a novel process; a novel process used to produce a range of products; organisms and derived products obtained by traditional breeding; and products, both viable and non-viable, obtained by genetic modification. The principal changes are the inclusion of exit points corresponding to products obtained by novel processes and products obtained synthetically from novel raw materials.” A specific consideration is given to exposure estimates. If submitted data is sufficient to determine that a new product will replace specific foods in the diet that are significant nutritional sources at significant levels for any groups in the population then nutritional evaluation is required.</td>
<td>This revision of the 1991 guidelines was based, in part, on the 1993 report by the Panel on Novel Foods discussed above. The criteria for exposure are limited only to novel foods that will replace nutritional sources in the diet at levels that would be significant to any group(s) in the population.</td>
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<td>Commission of the European Communities (1989)</td>
<td>Provided guidance for the composition of a “dossier” submitted in an application for assessment of new food additives prior to authorization. Technical data to be included are: name of substance, specifications (composition, empirical and structural formulas, molecular weight, degree of purity, nature of known impurities, physical forms, solubility, other relevant identifying characteristics). Additional information includes manufacturing process, methods of analysis, justification for use, exposure (frequency, duration, and other factors influencing exposure), variations affecting particular sections of the population such as age, sex, disease etc.), “reaction and fate in food (metabolism, by-products of storage and preparation, and any possible effect on nutrients. While the types of testing to be included in petitions was listed, no recommendations were offered as to criteria to ascertain the types of testing required as in Redbook. Sections on toxicological testing should include: acute toxicity, genetic toxicity, metabolic/pharmacokinetic testing, sub-chronic animal testing (two animal species, usually rodents and non-rodent) for 10% of the life span of the animals, reproduction and teratological testing, chronic toxicity, allergenicity, intolerance, and other “idiosyncratic” reactions. Human studies are recommended after “the safety of a new substance has been adequately demonstrated in animals...” Criteria for use of food additive (i.e., criteria for approval): - Petitioner can demonstrate a “reasonable technological need and the purpose cannot be achieved by other means which are economically and technologically practicable,” the additive presents “no hazard to health of the consumer at the level of use proposed, so far as can be judged on the scientific evidence available,” and the additive “does not mislead the consumer.” - The petitioner must provide evidence of “demonstrable advantages of benefit to the consumer”, i.e., a “need” as defined by four parameters: preservation of the nutritional quality of food, provision of foods for consumers with special dietary needs, enhancing or ensuring product quality and/or stability, and provide aids for the production of food. - The petition must account for potential additive or cumulative effects including potential synergistic or potentiating effects in combination with other elements in the food supply.</td>
<td>Criteria for testing approaches not supplied as in Redbook Concern Levels. Approval criteria include issues that are traditionally not considered by the FDA, e.g., the potential benefit of the new substance.</td>
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<td>Commission of the European Communities (1996)</td>
<td>An “opinion” focusing on information necessary to support application for “novel foods and novel food ingredients.” Document covers substances “which have not hitherto been used for human consumption to a significant degree...” and focused on six categories: substances containing or consisting of genetically modified (GM) organisms, substances produced from but not containing genetically modified organisms, substances with “a new or intentionally modified primary molecular structure”, substances consisting of or isolated from microorganisms, fungi or algae, substances “consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating and breeding practices and which have a history of safe use,” and substances “to which has been applied a production process not currently used where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism, or the level of undesirable substances.”</td>
<td>Significant emphasis on a case-by-case approach to these evaluations. Concept of substantial equivalence given significant weight in the description of the information required. The report also included coverage of “implications to human nutrition. Discussed the impact of high exposure estimates in the context of animal testing and application of traditional safety factors. “In the overall evaluation, it is of crucial importance to interpret carefully any adverse effects seen in animal studies and to distinguish between toxic effects and those due to nutritional imbalance in the experimental diet.” “In designing animal feeding studies, the maximum level of dietary incorporation achievable without causing nutritional imbalance should be the highest dose level, while the lowest dose level should be comparable to its anticipated role in the human diet.” “If the predicted usage levels and consumer intakes are likely to be high, the application of the traditionally calculated safety factors employed in safety assessment may create difficulties in designing conventional animal feeding studies with adequate dietary incorporation levels to ensure clearance for use in humans at the anticipated consumption levels. To compensate for the inability of employing reasonably adequate safety factors any sub-chronic or chronic animal feeding studies require supplementation by absorption and metabolism studies in animals and eventually humans.”</td>
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Addressed several key issues including substantial equivalence, compositional analysis, nutritional considerations, and requirements for toxicological testing. With regard to the latter, three criteria where delineated: is the substance substantially equivalent to an accepted traditional food or food ingredient (if yes, testing), can substantial equivalence be established “except for a single or few specific traits of the novel food...” (if yes, only those traits should be tested), and “neither partial nor total substantial equivalence can be established” in which case the “wholesomeness” of the substance has to be assessed using “an appropriate combined nutritional/toxicological approach.” In the latter case, factors that must be considered include; knowledge of identity, chemical structure and physico-chemical properties, source, composition, potential intake based on proposed conditions of use in human diets, potential exposure to vulnerable sub-populations, and the likely effect of processing.

Six scientific classes were identified for assessment of wholesomeness:
1) pure chemicals or simple mixtures from non-GM sources;
2) complex novel foods from non-GM sources;
3) GM plants and their products;
4) GM animals and their products;
5) GM microorganisms and their products; and,
6) Foods produced using a novel process.
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<tr>
<td>FDA (1982) “Redbook”</td>
<td>Contains guidelines for the premarket testing of new food ingredients. Testing based on derivation of concern levels (CL) determined from chemical structure and exposure estimates (per capita intake based primarily on industry based poundage estimates). Also contains a description of a process for continuous review of food ingredients including criteria, i.e., selection and ranking elements, to be used to decide on the need for postmarket testing.</td>
<td>Continues to serve as the guidance document for new food additive petitions.</td>
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<td>FDA (1993) “Redbook II”</td>
<td>As with the original Redbook, Redbook II was not an attempt to codify a list of mandatory tests, rather it was intended to provide guidance to petitioners. To date Redbook II has not been finalized. See Chapter 1 for a listing of the differences between Redbook and Redbook II. The draft version of the revised Redbook contained suggestions for assessing the safety of macro-additives, bioengineered additives, enzymes, and microbially-derived additives. The document also includes suggestions for alternatives to whole animal (vertebrate) testing.</td>
<td>This document is still in “draft” form and continues to undergo evaluation and revision.</td>
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<td>FDA (1997)</td>
<td>Supplemental document to the 1992 Statement of Policy: Foods Derived From New Plant Varieties: “The safety and nutritional assessment summary should contain sufficient information for agency scientists to understand the approach the firm has followed in identifying and addressing relevant issues.”</td>
<td>This was a guidance document based on comments received by the FDA.</td>
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<td>Health Canada (1995)</td>
<td>Proposal for the premarket clearance process for novel food products and processes. Novel foods defined as: - substances that have previously not been used as food in Canada or that have resulted from a new process - existing foods that &quot;have been modified by genetic manipulation and exhibit one or more characteristics that were previously not identified in that food, or food that results from production by a genetically manipulated organism exhibiting such characteristics.&quot; - food containing microorganisms previously not used in food or food processing. - food that is &quot;substantially modified form the traditional product or is manufactured by a process that has been substantially modified from the traditional process.</td>
<td>Aside from the definition of novel foods, this proposal contains little technical information.</td>
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<td>Joint UNEP/WHO (1987). (Environmental Health Criteria 70).</td>
<td>Coverage includes structure/activity relationships, exposures, human data, substances consumed in large amounts, chemical composition, nutritional and toxicity studies, foods from novel sources. Discussion of safety assessment of substances consumed in large amounts included chemical substances, modified food ingredients such as modified starches, and foods from novel sources. Describes differences in safety assessment from that of other food additives. Recommended approaches include data evaluation by JECFA, working groups of experts, responds to requests from other agencies. Included suggestion that modified food ingredients and foods from novel sources may require alternative methods of safety evaluation including chemical analysis, metabolic and nutritional studies, preclinical toxicity testing, and possible clinical studies and post-market monitoring. With regard to toxicological studies in animals the following statements were included: &quot;The establishment of a precise NOEL will not usually be feasible on account of the relative non-toxicity of high consumption additives and the impractibility of achieving an adequate safety margin between the NOEL in animals and the expected consumption of such substances by human beings.&quot; &quot;When establishing an ADI, the traditional concept of a 100-fold safety factor cannot operate when the human consumption level is high and feeding studies do not produce adverse effects (except for effects arising from the physical properties of the additive, such as its bulk and hydrophilicity), even when the substance is added to the diet in the maximum possible proportion, consistent with reasonable nutrition. In such cases new approaches are indicated, including setting the ADI on the basis of a smaller safety factor, which may be permissible when factors such as similarity to traditional foods, metabolism into normal body constituents, lack of overt toxicity, etc., are considered.&quot;</td>
<td>This document includes a seminal coverage of issues related to the safety assessment of new foods and food substances including those to be consumed in large amounts. A heavy emphasis was placed on the importance of nutritional and metabolic studies.</td>
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<td>Joint FAO/WHO Consultation (1991). World Health Organization, Geneva. Strategies for assessing the safety of foods produced by biotechnology.</td>
<td>The molecular, biological, and chemical nature of the material can identify need for animal toxicity studies; specific recommendations made for foods and food ingredients derived from genetically modified plants, animals, and microorganisms; classical animal toxicity testing may have limited application; mechanistic approaches to safety assessment are needed; evaluation should include both safety and nutritional value; comparative data on closest conventional counterpart should also be used.</td>
<td>The document provides useful working definitions of terms used in risk analysis. The discussion of sources of variability contributing to uncertainty throughout the risk analysis process it particularly helpful. Does not address new foods or new food substances.</td>
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<tr>
<td>Joint FAO/WHO Expert Consultation (1995). Application of Risk Analysis to Food Standards Issues</td>
<td>The intent of this document was to provide definitions of terms to be used in the application of risk analysis (defined as a process consisting of risk assessment, risk management, and risk communication) to the evaluation of food standards including food safety. Of relevance to the current report is the universe of things covered by these recommendations. Specifically, the Consultation considered foodborne agents to be &quot;chemical, biological and physical agents in or on food whether added intentionally or through natural processes.&quot; The following exclusion criteria were also included: &quot;live animals, food itself, or the natural components of food when present within normal limits.&quot; The Consultation notes that the ADI or the estimated amount of a food additive that can be ingested daily over a lifetime without appreciable health risk is based on the application of a safety factor to the NOAEL &quot;determined in the most appropriate (usually most sensitive) animal species.&quot; &quot;JECFA does not make a quantitative estimate of risk at an intake corresponding to the ADI, but concludes that the risk is so small as to be negligible from a public health point of view.&quot; The report contains an extensive discussion of the factors contributing to uncertainty at various stages of risk assessment.</td>
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Table 2-2. Positions of Various Authoritative Agencies on the Safety Evaluation of Genetically Modified Foods and Food Substances, including those Derived from Microbial Sources.

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<td>Buttershill, J. M. (1993)</td>
<td>An overview of the regulatory approach used in the UK to evaluate microbial enzymes. Consists of three core elements: a decision tree for deciding testing requirements, detailed provision of data for each new preparation, specifications for each preparation and provisions for adequate quality control. The committee responsible for these recommendations noted that “...the most appropriate way of subdividing microbial enzyme preparations should be based on the identity of the source material.” “The most important decision concerns whether toxicological data are required...”</td>
<td>This report is consistent with other statements by other organizations in emphasizing the importance of identifying source materials, production process, and, by implication, standards of identity in safety evaluations.</td>
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<td>Benbadis et al. (1995)</td>
<td>Focused on food products prepared with live microorganisms. In statement of principle, the group “agreed that absolute safety was impossible to establish for a new food product, but that it was possible to establish reasonable certainty of no harm to the consumer.” In cases where genetically modified organisms (GMO) were modified forms of organisms already in food, the preexisting organisms should serve as “a standard against which the GMO might be assessed”</td>
<td>This is the report of Working Group VII: food products. that met as part of a larger workshop “Risk Evaluation of Genetically Modified Microorganisms in Relation to Human Health.” This report was prepared for the EBC</td>
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<td>Commission of the European Communities (1996)</td>
<td>Scientific classification of novel foods for the assessment of wholesomeness. The document contains discussions of key issues for the assessment of novel foods and food ingredients such as genetically modified organisms, substantial equivalence, compositional analyses; nutritional considerations; toxicological requirements; implications of novel food to human nutrition; novel microorganisms used in food; allergenic potential; and assessment of marker genes.</td>
<td>See Table 2-1 for further discussion of this report.</td>
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<td>FDA (1992). Statement of Policy: Foods Derived From New Plant Varieties.</td>
<td>&quot;FDA's implementing regulations and current practice, utilizing an approach identical in principle to that applied to foods developed by traditional plant breeding.&quot; &quot;...the key factors in reviewing safety concerns should be the characteristics of the food product, rather than the fact that the new methods are used.&quot;</td>
<td>This notice does not apply to food and food substances that have been derived from algae, microorganisms, and other non-plant organisms including foods produced by fermentation, e.g., yogurt and single cell organisms, food ingredients produced by fermentation such as enzymes, flavors, amino acids, sweeteners, thickeners, antioxidants, preservatives, colors, substances produced from plants to be used as colors, substances produced from animals that are subject to FDA authority such as seafood, new drugs, new animal drugs, or pesticide chemicals (&quot;including those produced in plants as a result of genetic modification&quot;)</td>
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<td>&quot;Substances that are expected to become components of food as a result of genetic modification of a plant and whose composition is such or has been altered such that the substance is not generally recognized as safe (GRAS) or otherwise exempt are subject to regulation as 'food additives' under section 409 of the act.&quot;</td>
<td>The notice provides guidance with regard to specific questions to be asked by the producer before making a decision to market.</td>
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<td>&quot;In most cases, the substances expected to become components of food as a result of genetic modification of a plant will be the same as or substantially similar to substances commonly found in food, such as proteins, fats, and oils...&quot; &quot;FDA has determined that such substances should be subject to regulation under section 409 of the act in those cases when the objective characteristics of the substance raise questions of safety sufficient to warrant formal pre-market review and approval by FDA.&quot;</td>
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<td>FDA, 1993: “Redbook II”</td>
<td>The document includes a reference to the FDA Statement of Policy (see FDA, 1992, above).</td>
<td>The policy was summarized by Kessler et al. (1992) as follows:</td>
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<td>“Substances that have a safe history of use in food and substances that are substantially similar to such substances generally would not require extensive pre-market safety testing.” (Kessler et al. 1992).</td>
<td>Substances that raise safety concerns would be subjected to closer inquiry. This approach is both scientifically and legally sound and should be adequate to fully protect public health while not inhibiting innovation.”</td>
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<td>With regard to non-clinical safety testing of foods and food additives derived from genetically modified plants, Redbook II contains the additional reference to Kessler et al. (1992):</td>
<td>With regard to non-clinical safety testing of foods and food additives derived from genetically modified plants, Redbook II contains the additional reference to Kessler et al. (1992):</td>
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<td>“Animal feeding trials of foods derived from new plant varieties are not conducted routinely. However, in some cases testing may be needed to ensure safety. For example, substances with unusual functions or that will be new macro nutrients of the diet may raise sufficient concern to warrant testing. Tests could include metabolic, toxicological, or digestibility studies, depending on the circumstances.”</td>
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<td>FDA (1997)</td>
<td>Supplemental document to the 1992 Statement: intended to provide guidance to those developing genetically modified foods derived from new plant varieties on how to inform the agency &quot;about market entry plans.&quot; Specifically, the document contains descriptions on 1) an approach through which developers can consult with the agency, and 2) information on the procedures the Agency will use to evaluate these interactions.</td>
<td>This document focused on procedures in response to comments received by the FDA relative to its 1992 Statement of Policy.</td>
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<td>Health Canada (1994a). Food Directorate, Health Protection Branch (Vol.II)</td>
<td>The document covered both genetically modified plants and microorganisms, and contained the following general principles: &quot;A guiding principle in the safety assessment will be comparison of molecular, compositional and nutritional data for the modified organism to those of its traditional counterpart, where such exists. It is expected that once substantial equivalence to the existing food product can be established, no additional safety testing would be required. Where similarity or degree of equivalence cannot be established, a more extensive safety assessment may be necessary.&quot; &quot;In keeping with generally accepted approaches, the emphasis of the safety assessment will be on the product and not on the process used to develop it. However, to ensure that appropriate concerns are addressed, a clear understanding of the methods used to develop the product is necessary.&quot; &quot;Where appropriate, the basis for these safety assessments will be comparison of the molecular, compositional, toxicological, and nutritional data for the modified organism to those of its traditional counterpart.&quot;</td>
<td>Presentation on data relative to development and production of modified microorganisms and plants, including data needs regarding production, dietary exposure estimation, nutritional impact and toxicology.</td>
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<td>Health Canada (1995)</td>
<td>Expanded the definition of &quot;novel food&quot; to include those that have been genetically modified by genetic manipulation and exhibit one or more characteristics that were previously not identified in that food, or food that results from production by a genetically manipulated organism exhibiting such new characteristics.</td>
<td>The statement with regard to evaluating these substances on their own merits and &quot;not as a result of a process,&quot; is a departure from the decision tree approaches recommended by other agencies, e.g., the UK statements, in which both the source and the process were considered in the safety evaluation.</td>
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<td>Jacobsen et al. (1995)</td>
<td>A review of the general conclusions reached in a plenary session of the workshop, “Risk Evaluation of Genetically Modified Microorganism in Relation to Human Health,” conducted for the EEC. Among the key conclusions were: - &quot;all working groups agreed that the genetically modified organism should be evaluated on its own ground, as a product and not as a result of a process.&quot; - the participants stressed &quot;the need for a risk/benefit equation...&quot; because &quot;no risk assessment can ever cover all possible negative events.&quot; The group in recognizing that &quot;a benefit may outweigh recognized risks,&quot; also suggested that &quot;a comfort factor may also be taken in consideration, when there is an inevitable lack of complete information.&quot; - The attendees acknowledged &quot;the limitations of the present test systems both in terms of sensitivity and specificity...&quot;</td>
<td>The advocacy of a risk/benefit analysis is in conflict with current FDA policy relative to the evaluation of new foods and food substances. It was not clear whether the &quot;comfort factor&quot; was intended to serve the same role as uncertainty factors, i.e., an attempt to account for sources of variability.</td>
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<td>Metcalfe et al. (1996)</td>
<td>This compendium of eight articles on the allergenicity of foods produced by biotechnology was the result of a collaborative venture between the International Food Biotechnology Council (IFBC) &amp; the International Life Sciences Institute (ILSI). In addition to referenced reviews of issues such as an overview of immunology, food allergies, inherent components of foods and their allergic potential, the report contains a decision tree strategy proposed to ensure that new foods don't pose new threats. The core factor in the decision tree is the source material. If the substance is not derived from an allergenic source material, passes essentially the substantial equivalence test, and is stable during processing and digestion, it should not require additional testing and should be acceptable for marketing. The result of any deviations in these factors, leading to potential allergenicity required that the material be tested using standard immunological protocols. The option to the no concern decision is a labeling requirement prior to marketing. The decision tree does not have a disapproval contingency.</td>
<td>The editors included a consideration of the use of animal testing to evaluate the potential allergenicity of new foods and concluded that “animal models are valuable for mechanistic and exploratory studies, but...at the present time no reliable animal models are available that are generally predictive of the allergic potential of foods for humans.”</td>
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<td>Organization for Economic Cooperation and Development (OECD) (1993)</td>
<td>This is a report of the Working Group on Food Safety of the Group of National Experts on Safety in Biotechnology. The group was asked to address five core issues: scientific principles to be applied to the definition of new foods or food components, identification of methods to distinguish between a new substance and its conventional counterpart, the applicability of conventional approaches to safety assessment for the evaluation of new substances, methods for establishment of substantial equivalence, methods for safety evaluation of novel substances, i.e., those lacking a conventional counterpart. The focus of the conclusions of this report was on the determination of substantial equivalence; &quot;...knowledge that a new food or food component(s) was derived from organism(s) whose newly introduced traits have been well-characterized, together with a conclusion that there is reasonable certainty of no harm as compared with its conventional or traditional counterpart, means that a new food or food component(s) can be considered substantially equivalent.&quot; &quot;If a new food component is found to be substantially equivalent to an existing food or food component, it can be treated in the same manner with respect to safety. No additional safety concerns would be expected.&quot; &quot;Where substantial equivalence is more difficult to establish because the food or food component is either less well-known or totally new, then the identified differences, or the new characteristics should be the focus of further safety considerations.&quot;</td>
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<td>The report included case study presentations of various types of foods and food components. The scope of the recommendations did not cover: - safety evaluation of food additives, contaminants, processing aids or packaging materials - evaluations of environmental impact - new foods or food components other than those of &quot;terrestrial microbial, plant, or animal origin.&quot; The focus on substantial equivalence essentially echoes the FDA's current position.</td>
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<td>Organization for Economic Cooperation and Development (OECD) (1995)</td>
<td>The focus of this effort was to develop strategies to establish safety of foods derived from biotechnology when there is no acceptable counterpart for comparison, i.e., when substantial equivalence cannot be established. Papers presented covered such topics as appropriate uses of traditional methods, substantial equivalence, analytical studies, databases, in vitro and in vivo testing, dietary assessments in safety evaluation of new foods, allergenicity, safety of using microorganisms in food processing, and the presentation of several case studies. The report of the working group sessions contained the following summary conclusions: - reaffirmed the importance of the substantial equivalence standard presented in the 1993 OECD report. - &quot;when the product is substantially equivalent to a traditional counterpart except for the inserted trait, it was concluded that further safety assessment should focus on the product of the inserted gene.&quot; The report included a listing of characteristics that should be evaluated relative to the inserted gene, e.g., source, identity, effect, digestibility, stability of the trait, etc. - With regard to substances found to be not substantially equivalent, the group noted that, &quot;Just because a new food is not substantially equivalent to an existing food does not mean that it is less safe but that safety testing that would be required should be based on the properties of the new food.&quot; - the group acknowledged the inherent difficulties in testing foods in animals. &quot;Animal feeding studies in general are not sensitive enough to detect unintended effects as a result of gene modification. Therefore, if animal studies are considered necessary, there is a need to modify existing protocols for testing food or food components, in particular, by providing adequate nutrition with respect to diet; the usual concept of safety margins may not be applicable&quot;</td>
<td>A continuation of discussions of issues addressed in the 1993 report, the focus was on principles to be followed in testing new foods and food substances. The conclusions of the group did not provide specific guidance but reinforced the need to perform evaluations on a case-by-case basis and the importance of accurate characterization of new materials.</td>
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<td>Committee on Medical Aspects of Food Policy. Panel on Novel Foods (1993). Department of Health, U.K.</td>
<td>Defined genetic modification as the identification, extraction, and insertion of genes that code for a particular desired characteristic. This Panel echoed the findings in the report from the WHO (1991) acknowledging that transgenesis, i.e., the process of introducing DNA from one species into the genome of another, “should not cause any significant concern” in terms of food safety. However this Panel did consider that “food intolerance and allergies might be a potential hazard.” The Panel also stated that “potential nutritional significance of genetic modifications to the food supply is, at present, uncertain. Nevertheless, the Panel considered that transgenesis has the potential to produce food with a significantly altered nutritional composition or quality, which should be monitored from a nutritional perspective.” In its statement of general principles, the PNF recommended that “foods derived from genetically modified sources should be assessed in a similar manner to those produced by conventional techniques.”</td>
<td>The report includes a brief description of how foods and food substances are regulated in the UK: All foods including novel foods are currently controlled in the UK under the provisions of the Food Safety Act of 1990. Premarket clearance of novel foods and food processes is not part of the Act and is voluntary; manufacturers are therefore free to market their products subject only to the requirements of the Act but are encouraged to submit for clearance. “Clearance of a food or food process does not constitute formal approval, rather it is a confirmation that on the evidence presented, Ministers see no food safety reason why the food should not be legally marketed in the UK.”</td>
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<td>Joint FAO/WHO Consultation. World Health Organization (1991). Strategies for assessing the safety of foods produced by biotechnology.</td>
<td>A presentation of strategies and procedures to assist in assessing the safety of specific applications of biotechnology in food production and processing including plants, animals, bacteria, and fungi. The molecular, biological, and chemical nature of the material can identify need for animal toxicity studies; specific recommendations made for foods and food ingredients derived from genetically modified plants, animals, and microorganisms; classical animal toxicity testing may have limited application; mechanistic approaches to safety assessment are needed; evaluation should include both safety and nutritional value; comparative data on closest conventional counterpart should also be used.</td>
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<td>Joint FAO/WHO Consultation, No. 61, Rome, Italy (1996)</td>
<td>The report contains an expansive discussion of the question of substantial equivalence defined as follows: &quot;Substantial equivalence is established by a demonstration that the characteristics assessed for the genetically modified organism or the specific food product derived therefrom, are equivalent to the same characteristics of the conventional comparator. The levels and variation for characteristics in the genetically modified organism must be within the natural range of variation for those characteristics considered in the comparator and be based upon an appropriate analysis of the data.&quot; Three contingent outcomes were listed as a result of a comparison with a conventional substance: substantial equivalence, substantial equivalence except for specific differences, and not substantially equivalent. The Consultation emphasized that &quot;the safety assessment of proteins should focus on the structure, function, and specificity of the protein(s) and its history of use in foods, if any.&quot; Guidance was provided as to how such structure/function/specificity assessments might proceed. Among the elements to be considered in the assessment of substantial equivalence are the molecular characterization of the food source, phenotypic characteristics of the new food source in comparison to an appropriate comparator already in the food supply, and compositional analysis of the new substance compared to the conventional counterpart. Specific components of each of these comparison elements were described. The report also contained specific recommendations about allergenicity. (See Chapter II of this report for complete listing)</td>
<td>This report on biotechnology and food safety expanded on many of the issues discussed in the previous consultation as well as the OECD reports discussed herein. The report also included specific recommendations with regard to testing for allergenicity of genetically modified foods.</td>
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<td>World Health Organization (1993). Health Aspects of Marker Genes in Genetically Modified Plants. Report for a WHO Workshop. World Health Organization, Geneva.</td>
<td>Summary presentations were made on “The role of marker genes in plant biotechnology,” and “Safety issues arising from the use of marker genes in plant biotechnology,” Among the conclusions reached by the Workshop attendees were the following:</td>
<td>Marker genes were defined as “genes used to identify cells or plants during the selection of plant varieties.” The workshop considered several classes of marker genes including: antibiotic resistant genes, herbicide tolerance genes, and “those that could be used in other selection systems and those that are screenable marker genes, such as color markers.”</td>
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<td>- “the presence of marker genes per se in food would not constitute a safety concern.”</td>
<td>The workshop attendees endorsed the application of the safety assessment strategies outlined by FAO/WHO and OECD for genetically modified plants varieties to the assessment of plants containing marker genes. They also recognized in general terms, “the principles established for assessing the human food safety of genetically modified plants,” as being “applicable for the assessment of the safety of genetically modified plants used for animal feed.”</td>
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<td>- “...in assessing the safety of the proteins expressed by marker genes used in plant biotechnology, the focus of the assessment should be on the function of the expressed protein rather than its structure.”</td>
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<td>- “...there is no reason to suppose that marker gene proteins pose a particular allergenic concern. However, if the genes are obtained from a source known to cause food allergy, the allergenicity of the gene product will need to be investigated.”</td>
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<td>- “...there are no characteristics of marker genes or their products that suggest that their site of insertion into the plant genome will give rise to additional secondary and/or pleiotropic effects.”</td>
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<td>- “...there is no recorded evidence for the transfer of genes from plants to microorganisms in the gut. If transfer did occur, any health concern would depend on many factors, including the ability of the transformed microorganisms to replicate in the gut and the express the gene product. Unless the transferred gene was under the control of bacterial promoters (and thus not expressed in the plant) there was no mechanism for expression in gut bacteria.”</td>
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<td>- “...specific strategies would need to be applied to different categories of marker genes...”</td>
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<td>- “...the presence or absence of marker genes in food could not be correlated reliably with the presence or absence of recombinant DNA. Hence, while the detection of marker genes might provide a possible screening test for the presence of genetically modified plants in food, the results of such tests would need to be interpreted with caution.”</td>
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regard to the safety evaluation of new foods and food substances and genetically modified foods and food substances, respectively. The following is a brief review of some of the positions on safety assessment considered most relevant by the Expert Panel.

1. Guidelines and positions about novel foods and food substances

A seminal report addressing many of the key issues associated with the safety evaluation of new foods and food ingredients is the report entitled “Principles for the Safety Assessment of Food Additives and Contaminants in Food” by the Joint UNEP/IOI/WHO Committee (1987). A significant emphasis was placed on the importance of nutritional and metabolic studies in the evaluation of substances to be consumed at high concentrations in the diet. While outlining many of the key features separating substances consumed at high concentrations from traditional food additives, the report also included statements about the problems associated with the use of traditional approaches to safety evaluation of such materials.

For example, with regard to the establishment of a NOEL the committee stated, “The establishment of a precise NOEL will not usually be feasible on account of the relative non-toxicity of high consumption additives and the impracticability of achieving an adequate safety margin between the NOEL in animals and the expected consumption of such substances by human beings.”

The committee also noted the problems inherent in the use of traditional uncertainty factors for the generation of an ADI for substances to be consumed in high amounts. “When establishing an ADI, the traditional concept of a 100-fold safety factor cannot operate when the human consumption level is high and feeding studies do not produce adverse effects (except for effects arising from the physical properties of the additive, such as its bulk and hydrophilicity), even when the substance is added to the diet in the maximum possible proportion, consistent with reasonable nutrition. In such cases new approaches are indicated, including setting the ADI on the basis of a smaller safety factor, which may be permissible when factors such as similarity to traditional foods, metabolism into normal body constituents, lack of overt toxicity, etc., are considered.”

In a process similar to that of the FDA in its promulgation of the original Redbook and subsequent revisions, the United Kingdom (UK) has provided guidance to those intending to introduce a new food or food substance to the food supply. In 1984, the Advisory Committee on Irradiated and Novel Foods (ACINF) of the Ministry of Agriculture, Fisheries, and Food (MAFF), issued a “Memorandum on the Testing of Novel Foods.” The ACINF was subsequently renamed the Advisory Committee on Novel Foods and Processes (ACNFP) and issued a revision of its earlier memorandum in 1991 (Table 2-1). As with the Redbook, the goal of the ACNFP documents is to give guidance to the food industry on the sort of information it would wish to see in any submission for a novel food, food substances, or process (ACNFP, 1991).

In the 1991 report, a food was defined as “novel” if it is “the result of the use of novel raw materials, novel processing, or preparation techniques or novelty of its role in the diet. Novel food, organisms, or products derived from such organisms may result from recently developed techniques such as genetic modification or from more conventional plant and animal breeding techniques.” The definition was further refined to state that “novel foods are foods or food ingredients which have not hitherto been used for human consumption to a significant degree in the United Kingdom and/or which have been produced by extensively modified or entirely new food production processes.” This definition was intended to cover “all foods intended for UK consumers which may be marketed in a form or manner that could bring about significant nutritional changes in the diet.” The definition did not cover food additives, including flavoring and processing aids, components extracted from conventional foods by traditional processes, recipe changes or minor process modifications. The definition did cover living organisms added to food such as starter cultures. The ACNFP noted that “while it is not possible to give comprehensive guidance on the type of products or processes to be referred, food produced by technology such as genetic modification and synthetic food items such as certain fat replacers will be of particular interest.”
A novel process was defined as "...a process which has not hitherto been used in the processing of foods." The definition was "intended to cover processes which could bring about significant toxicological or nutritional changes in the food."

In the decision tree presented by ACNFP (1991), foods not produced from a novel raw material or process and having no novel use were not considered novel. The amount of testing increased depending on the root material, production process, and use with foods being categorized as A through R. For example, a food considered novel based only on its use (category A) would require only nutritional testing in humans (with special emphasis on high-risk groups such as children or those relying on institutional food) and animals (if necessary to determine metabolizable energy, protein quality, if applicable, and vitamin and mineral bioavailability). Recommended testing for a novel food resulting from a novel process (category B) included exposure estimation, technical details of processing and product specifications, nutritional studies, and toxicological assessment. The amount and type of testing increased in complexity in novel foods produced from a novel raw material, with the most elaborate testing recommended for live genetically modified organisms, category R. This latter recommendation is similar (albeit significantly more detailed) to the position stated in Redbook II, which includes the following statement regarding microbiologically derived food ingredients: "A unique concern about the safety of microbiologically derived food ingredients is the microbial source; except for this concern, the safety of these ingredients will be evaluated as for analogues, non-microbiologically derived ingredients" (FDA, 1993).

It should be noted that although the emphasis of the ACNFP decision tree was on the source, process, and use of novel foods and food substances, there was only a brief discussion of the problems associated with high exposure estimates for these new products. In the discussion on toxicological testing, the ACNFP (1991) acknowledged that "the traditional method of assessing the safety of a food additive, i.e., allowing a one hundred-fold margin between the maximum amount of the additive likely to be consumed in the human diet and the maximum amount which has no toxic effect when fed to animals, clearly cannot be applied to a food which would constitute more than one per cent of the human diet." Aside from acknowledging this problem, the ACNFP offered no solutions to this dilemma other than suggesting that "due to the complex nature of foods, there is a need to balance test and control diets for both major and minor constituents."

In the intervening years, ACNFP has continued to examine issues relevant to the safety evaluation of novel foods and food substances. In 1992, the Panel on Novel Foods (PNF) of the Committee on Medical Aspects of Food Policy was convened to examine issues related specifically to Olestra, and more generally to discuss the nutritional evaluation of novel foods and food substances. The deliberations of the PNF resulted in the report "The Nutritional Assessment of Novel Foods and Processes" (Committee on Medical Aspects of Food Policy, 1993).

Based in part on this report as well as input from other advisory committees, the ACNFP revised its guidelines (ACNFP, 1994) with the release of "A Structured Approach for the Safety Assessment of Novel Foods and Processes: Revision to Chapter 4 of the ACNFP's Guidelines." (Table 2-1).

The Commission of the European Communities (1989) has offered guidance on the materials needed to assess the safety of novel foods. In this report, the Commission delineated its criteria for use of food additives (i.e., criteria for approval):

- If the petitioner can demonstrate a "reasonable technological need and the purpose cannot be achieved by other means which are economically and technologically practicable," the additive presents "no hazard to health of the consumer at the level of use proposed, so far as can be judged on the scientific evidence available," and the additive "does not mislead the consumer."

- The petitioner must provide evidence of "demonstrable advantages of benefit to the consumer," i.e., a "need," as defined by four parameters: preservation of the nutritional quality of food, provision of foods for consumers with special dietary needs, enhancing or ensuring product quality and/or stability, and aiding in the production of food.
The petition must account for potential additive or cumulative effects including potential synergistic or potentiating effects in combination with other elements in the food supply.

It is of particular interest to note that aside from the issues related to safety, i.e., “no hazard to health of the consumer at the level of use proposed, so far as can be judged on the scientific evidence available,” and the question of the potential additive effects of new substances, the other criteria, i.e., justification based on need or potential benefits, are not considered in the FDA’s guidance documents.

In 1996, the European Commission offered an “opinion” paper focused on the safety evaluation of six categories of novel foods and food substances: substances containing or consisting of genetically modified (GM) organisms, substances produced from but not containing genetically modified organisms, substances with “a new or intentionally modified primary molecular structure”, substances consisting of or isolated from microorganisms, fungi or algae, substances “consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating and breeding practices and which have a history of safe use,” and substances “to which has been applied a production process not currently used where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value metabolism, or the level of undesirable substances” (The Commission of the European Communities, 1996).

A focal point of the discussion in the 1996 report was the concept of substantial equivalence. Although emphasizing that “establishment of substantial equivalence is not a safety or nutritional assessment in itself, but an approach to compare a potential new food with its conventional counterpart,” the Commission did use this concept as the core element upon which to base the decisions about the need for toxicological testing. The three criteria delineated for making such decisions were:

- whether the substance is substantially equivalent to an accepted traditional food or food ingredient (if yes, no testing),
- when substantial equivalence can be established “except for a single or few specific traits of the novel food... (if yes, the safety evaluation should focus only on those differences), and
- when “neither partial nor total substantial equivalence can be established” the “ wholesomeness” of the substance has to be assessed using “an appropriate combined nutritional-toxicological approach.”

In the latter case, factors that must be considered include knowledge of identity, chemical structure and physicochemical properties, source, composition, potential intake based on proposed conditions of use in human diets, potential exposure to vulnerable sub-populations, and the likely effect of processing.

2. Guidelines and positions about genetically modified foods and food substances

Table 2-2 contains a brief summary of some of the positions and guidelines available for the assessment of foods and food substances derived from genetic modification. A brief discussion of those documents follows.

As mentioned, the FDA is currently revising its “Redbook.” In addition to guidance for the safety evaluation of traditional food additives, Redbook II (FDA, 1993) contains suggestions for data to be used for the assessment of macroingredients, bioengineered additives, enzymes, and microbially derived additives. Among the suggestions are alternatives to whole animal testing. In addition, the FDA has published a statement of its policy on foods derived from new plant varieties (FDA, 1992). The positions stated in this notice are outlined in Table 2-2.

Several key elements of the FDA’s position on genetically modified foods of plant origin are germane to the topic of this report:
"...the key factors in reviewing safety concerns should be the characteristics of the food product, rather than the fact that the new methods are used."

Substances that are expected to become components of food as a result of genetic modification of a plant and whose composition is such or has been altered such that the substance is not generally recognized as safe (GRAS) or otherwise exempt are subject to regulation as ‘food additives’ under section 409 of the act.

"In most cases, the substances expected to become components of food as a result of genetic modification of a plant will be the same as or substantially similar to substances commonly found in food, such as proteins, fats, and oils..." "FDA has determined that such substances should be subject to regulation under section 409 of the act in those cases when the objective characteristics of the substance raise questions of safety sufficient to warrant formal premarket review and approval by FDA."

The key component in the FDA’s approach to evaluation of genetically modified foods and food substances of plant origin is the accurate characterization of the properties of the new material in order to establish substantial equivalence. As will be seen in the review of positions of other agencies, the concept of substantial equivalence is a fundamental unifying principle supporting all recommendations regarding the evaluation of these new products.

Health and Welfare Canada (1989) sponsored a symposium on “Approaches to Assessing the Safety of Crops Developed Through Wide-Cross Hybridization Techniques.” Both traditional plant breeding practices and biotechnologic (genetic engineering) systems were considered. A 16-member expert panel noted that current developments have already exceeded routine methods for toxicologic assessment and offered the following recommendations on provisions for assessing the potential of a new variety to affect public health adversely:

- responsible government agencies should monitor the potential of new varieties to produce significant changes in nutritional and toxicological qualities of foods produced;

- developers must provide adequate chemical analyses of both the new variety and the product to be replaced; and

- the government should develop standards and analytical parameters for such analyses.

The review and revision process has culminated in a final proposal published in 1995 that covers the safety evaluation of all novel foods and food substances proposed for use in Canada (Health Canada, 1995). In this document, novel foods are defined to include those that have been genetically modified by genetic manipulation and exhibit one or more characteristics that were previously not identified in that food, (i.e., do not meet the standard of substantial equivalence), or food that results from production by a genetically modified organism exhibiting such new characteristics. This proposal is philosophically consistent with the FDA’s statement of policy relative to genetically modified foods of plant origin (FDA, 1992).

In 1993, the Working Group on Food Safety of the Group of National Experts on Safety in Biotechnology of the Organization for Economic Cooperation and Development (OECD) published a report containing the proceedings of the first of two workshops focusing on the safety evaluation of new foods and food substances, particularly those derived from genetic modification (OECD, 1993). The group was asked to address five core issues: scientific principles to be applied to the definition of new food or food component, identification of methods to distinguish between a new substance and its conventional counterpart, the applicability of conventional approaches to safety assessment for the evaluation of new substances, methods for establishment of substantial equivalence, and methods for safety evaluation of novel substances, i.e., those lacking a conventional counterpart.

The working group reached the following conclusions:
The determination of substantial equivalence is the essential component in the determination of the need for testing for a new food or food substance. Substantial equivalence was defined as "...knowledge that a new food or food component(s) was derived from organism(s) whose newly introduced traits have been well-characterized, together with a conclusion that there is reasonable certainty of no harm as compared with its conventional or traditional counterpart...."

"If a new food component is found to be substantially equivalent to an existing food or food component, it can be treated in the same manner with respect to safety. No additional safety concerns would be expected."

"Where substantial equivalence is more difficult to establish because the food or food component is either less well-known or totally new, then the identified differences, or the new characteristics should be the focus of further safety considerations."

In September 1994, a Workshop on Food Safety Evaluation sponsored by the OECD was held at Oxford, England and attended by over 50 participants from 17 OECD countries and the European Economic Community (OECD, 1995). The primary purpose of the meeting was to identify strategies to be used to establish the safety of food produced by biotechnology when there is no acceptable counterpart for comparison. The workshop organizers chose to expand its scope to consider experiences with novel foods from nonbiotechnological sources, as well as experiences with biotechnologically based foods with conventional counterparts, leading, hopefully, to a basis for an approach to the safety assessment of any foods without conventional counterparts.

The proceedings included 18 presentations on topics ranging from toxicological testing of irradiated foods, substantial equivalence in toxicological testing of novel foods, and limitations of feeding trials focused on whole foods, to the use of human-type diets in rodent feeding studies. Food safety assessment parameters considered by the workshop included detailed treatment of the concept of substantial equivalence, analytical studies, data bases, in vitro and in vivo testing, allergenicity, and the safety and acceptability of using microorganisms in food production.

The report of the working group sessions contained the following summary conclusions:

• A reaffirmation of the importance of the substantial equivalence standard presented in the 1993 OECD report.

• A statement about the criteria for establishing the need for safety assessment: "When the product is substantially equivalent to a traditional counterpart except for the inserted trait, it was concluded that further safety assessment should focus on the product of the inserted gene."

• A listing of characteristics that should be evaluated relative to the inserted gene, e.g., source, identity, effect, digestibility, stability of the trait, etc.

• With regard to substances found to be not substantially equivalent, the group noted that "Just because a new food is not substantially equivalent to an existing food does not mean that it is less safe but that safety testing that would be required should be based on the properties of the new food."

• The group acknowledged the inherent difficulties in testing foods in animals. "Animal feeding studies in general are not sensitive enough to detect unintended effects as a result of gene modification. Therefore, if animal studies are considered necessary, there is a need to modify existing protocols for testing food or food components, in particular, by providing adequate nutrition with respect to diet; the usual concept of safety margins may not be applicable "

In September of 1996, the FAO/WHO held a joint consultation on biotechnology and food safety that included a further expansion of the concept of substantial equivalence (FAO/WHO, 1996). Emphasizing that the "establishment of substantial equivalence is not a safety assessment in itself, but a dynamic, analytical exercises in the assessment of the safety of a new food relative to an existing food," the Consultation provided further guidance with respect to the key
elements required to make such a determination. It was noted that the "reference characteristics for substantial equivalence comparisons need to be flexible and will change over time in accordance with the changing needs of processors, and consumers, and with experience."

The Consultation offered the following definition of substantial equivalence: "Substantial equivalence is established by a demonstration that the characteristics assessed for the genetically modified organism or the specific food product derived therefrom, are equivalent to the same characteristics of the conventional comparator. The levels and variation for characteristics in the genetically modified organism must be within the natural range of variation for those characteristics considered in the comparator and be based upon an appropriate analysis of the data.

Three possible outcomes of the process to determine substantial equivalence were identified:

- the genetically modified organism, or a food or food component derived from it, is substantially equivalent to a conventional counterpart already available in the food supply.

- the genetically modified organism or food/component derived form it is substantially equivalent to its conventional counterpart with the exception of certain defined differences. The report includes a description of the types of differences that might occur, for example different proteins or unexpected substances produced as a result of the genetic modification, and a delineation of how those differences might be evaluated. The Consultation emphasized that "the safety assessment of proteins should focus on the structure, function, and specificity of the protein(s) and its history of use in foods, if any." Guidance was provided as to how such structure/function/specificity assessments might proceed.

- the genetically modified organism or food/component is not substantially equivalent to its conventional counterpart "either because differences are not sufficiently well-defined or because there is no appropriate counterpart with which to make a comparison."

Among the elements to be considered in the assessment of substantial equivalence of a food product (either a food source or the specific food product) are the molecular characterization of the food source, phenotypic characteristics of the new food source in comparison to an appropriate comparator already in the food supply, and compositional analysis of the new substance compared to the conventional counterpart. Specific components of each of these comparison elements were described.

The report also contained the following four specific recommendations with regard to allergenicity:

- "The transfer of genes from commonly allergenic foods should be discouraged unless it can be documented that the gene transferred does not code for an allergen.

- Foods found to contain an allergen transferred from the organism which provided the DNA should not be considered for marketing approval unless such products can be clearly identified in the marketplace and this identity will not be lost through distribution and processing. Further, that labeling approaches may not be practical in these situations, and that particular problems exist for consumers who cannot read, or who may not be provided with labels.

- involved organizations should consider the appropriateness of, and/or actions to take, in respect to foods containing new protein(s) that are determined to have the characteristics of an allergen, even though no patient population is known to exist which has an allergy to this gene product.

- the identification of food allergens and characteristics of these allergens that define their immunogenicity be encouraged."
3. **Related issues**

The Expert Panel also noted a recent effort at standardization of toxicological methodologies conducted by the Interagency Coordinating Committee on Validation of Alternative Methods (NIEHS, 1997) in response to two new mandates of the NIH Revitalization Act of 1993 to (a) establish criteria for validation and regulatory acceptance of alternative testing methods and (b) recommend processes for regulatory acceptance of new methods. This report which was the result of a workshop involving representatives from all of the Federal regulatory agencies, including the FDA, contained criteria for validation and regulatory acceptance of alternative toxicological testing methods. The suggested process includes use of a committee of experts, collection of data, review and evaluation of alternate methods, and presentation of draft report to OECD.

4. **Summary**

Clearly, a significant amount of time and intellectual capital has been invested in trying to establish principles and criteria for the evaluation of new foods and food substances. There are some areas of universal agreement, for example, the traditional approach to toxicological testing of new foods and food substances is often not appropriate because of the estimated exposure of the substances, the nature of the source materials and the process used to produce them. With regard to genetically-modified substances, the concept of substantial equivalence appears to be a cornerstone of most of the approaches recommended for the evaluation of such products. The Expert Panel recognized the contributions of these documents and used them as reference and support in its deliberations.
III. CONCEPTUAL FRAMEWORK FOR THE SELECTION OF TRADITIONAL OR ALTERNATIVE APPROACHES TO SAFETY EVALUATION OF NEW FOOD INGREDIENTS

A. COVERAGE OF THE REPORT

1. The continuum of substances to be evaluated

As stated in Chapter I, the Expert Panel recognized that the universe of substances that will be covered by its recommendations and whose uses are regulated by the FDA is a continuum that ranges from traditional food additives, i.e., those of some known chemical identities with a low exposure estimate, to those novel ingredients and "new foods" that may constitute a significant portion of the diet. From a regulatory perspective, this continuum might begin at one end with indirect food additives and conclude with foods. Irrespective of the source or nature, all of these substances will need to meet the same standard of safety, "reasonable certainty of no harm."

In seeking ways to define the universe of materials covered by its recommendations, the Expert Panel sought the insight of other individuals and organizations. For example, in 1959, the National Academy of Sciences-National Research Council Food Protection Committee (Food Protection Committee, 1959. Principles and procedures for evaluating the safety of food additives. NAS-NRC Pub. No. 750. Washington D.C.) defined a food additive as "...a substance or mixture of substances, other than a basic food stuff, which is present in food as a result of any aspect of production, processing, storage, or packaging. The term does not include chance contaminants." Although reasonably inclusive in terms of materials added to foods, for the purposes of this report, this definition does not offer a full coverage of the materials identified in the Scope of Work.

In presenting this problem in the Scope of Work, the FDA identified the types of substances that might be considered to require an "alternative" approach. Examples given were substances resulting from "the advent of new technologies such as genetic engineering of traditional foods, and novel uses of plant products, as well as development of macroingredients..." (FDA, 1996). More specifically, the Expert Panel recognized that the universe of substances for which the FDA has responsibility for safe use includes substances appearing in human diets:

1) at a wide range of concentrations, (e.g., flavors and indirect food additives used at low concentrations; sugars, starches, and gums used at intermediate concentrations; and, macro ingredients and whole foods present at high concentrations), and

2) with a wide range of toxic potential (e.g., starches with low toxic potency and trace minerals and some vitamins with relatively high toxic potential)

For substances with a simple chemical composition, produced by a well-recognized method from well-characterized materials and present in the diet at low concentrations (e.g., flavoring agents), protocols for assessing risk are well defined and carry a relatively high degree of confidence in most cases. However, for substances with a complex composition, produced by novel methods from new materials and/or those used in the diet at high concentrations, traditional testing protocols are often unsatisfactory and necessitate the use of alternative approaches. More specifically, the Expert Panel was aware of several efforts both domestically (e.g., Redbook II; FDA, 1993) and internationally (e.g., the UK decision tree for novel foods; Advisory Committee on the Assessment of Novel Foods and Processes; ACNFP; 1991, 1994) that have addressed issues pertaining to testing requirements necessitated by

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1 The Expert Panel defined complex substances as those that are chemically heterogeneous, and either do not pass the test of substantial equivalence or provide an obvious frame of reference for such comparisons as described in the structure categorization process outlined in Redbook (FDA, 1982).
increasingly complex new foods and food substances derived from novel sources. However, for the most part, these efforts have not dealt in any great detail with such specific issues as the impact of estimated high levels of exposure, that can occur in any of these new materials irrespective of source or complexity, on the ability to conduct traditional animal based toxicology tests.

Consequently, because many new materials might be projected to occur at sufficiently high concentrations in the diet or be sufficiently different in nature from currently accepted foods or food substances to warrant a reexamination of the appropriateness of the traditional approach, the universe of substances to be covered by the Panel's recommendations include:

- Whole foods that do not have a history of use in the United States;
- new macrofood ingredients;
- food ingredients approved for a specific use at a dietary concentration less than the critical concentration, i.e., 0.1%\(^2\), but for which a new use, that exceeds the critical concentration is proposed,
- food ingredients approved for a specific use at dietary concentrations exceeding 0.1%, but for which a new use that also exceeds 0.1% is proposed;
- naturally occurring substances with no history of use in the U.S. or for which new or more extended use is proposed;
- foods containing microorganisms not previously sanctioned for use in U.S. diets;
- foods and food substances consisting of, or isolated from, microorganisms, fungi, or algae;
- foods and food substances exposed to a new process that causes significant changes in composition or structure, which, in turn, result in decreased nutritive value, altered metabolism or an increased concentration of undesirable components;
- conventional organisms, ingredients, or foods that have been chemically modified;
- genetically modified organisms, substances, or foods; and
- products from genetically modified organisms.

As noted in Chapter II, other organizations have attempted to address the problems associated with these novel substances. The report of the Joint U.N. Environment Programme, International Labour Organization and WHO (Joint UNEP/ILO/WHO, 1987) delineated six reasons why substances consumed in large amounts would require a safety assessment that, "should differ from that of other food ingredients, such as coloring and flavoring agents, and antioxidants . . .":

- "Many will have a high daily intake and, thus, minor constituents and processing impurities assume greater than usual significance;"

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\(^2\) This concentration was chosen as a reference point because substances present at concentrations >0.1% cannot be evaluated in animal trials using the 100:1 uncertainty factor approach (assumes that tests conducted using the substance at a dietary concentration >10% will lead to results that are not meaningful).
• Even though they are often structurally similar or even identical to natural products used in food and thus may appear to be of low toxicity, many may require extensive toxicity testing because of their high daily intake;

• Some may be metabolized into normal body constituents;

• Some substances, particularly foods from novel sources, may replace traditional foods of nutritional importance in the diet;

• Many are complex mixtures rather than defined chemical substances; and,

• The difference between the quantity that can be fed to animals in feeding tests and the amount consumed by human beings is often relatively small."

The Panel on Novel Foods of the Committee on Medical Aspects of Food Policy of the U.K. (Committee on Medical Aspects of Food Policy, 1993) defined novel foods as those that "may be modified food components, synthetic substances, or new raw materials that are derived from animals, plants, or microorganisms."

With regard to questions raised by the advent of new type of foods and food substances, the Expert Panel considered many issues, for example:

• "Substantial Equivalence": As noted in Chapter II, several other organizations, e.g., OECD (1993, 1995), Commission of the European Communities (1996), the Joint FAO/WHO Consultation (1996) have used the standard of substantial equivalence as a cornerstone for recommendations about the need for testing of new products particularly those derived as a result of genetic modifications.

With regard to substantial equivalence, the Expert Panel agreed on two principles:

1) The Expert Panel concurred with the statement of the European Commission (1996) that, "the establishment of substantial equivalence is not a safety or nutritional assessment in itself, but an approach to compare a potential new food with its conventional counterpart." This rubric focuses attention on the selection of an appropriate control substance, an issue discussed in greater detail later in this chapter and in Chapter IV.

2) The Expert Panel agreed with the position of the Joint FAO/WHO Consultation (1996) that the determination of substantial equivalence relative to new foods requires a consideration of the molecular characteristics of the new food source, phenotypic characterization of the new food source in comparison to an appropriate comparison food already in the food supply, and a compositional analysis of the new food in comparison to preexisting comparison food. In cases of new substances that might have an equivalent composition, if the substance is derived from a different genetic source than the comparison acceptable food, then the new substance would not meet the standard and would require testing to ensure that it meets the standard of safety, i.e., reasonable certainty of no harm.

The Expert Panel utilized the following definition for "substantial equivalence":

Any substance that is essentially identical in terms of phenotypic characteristics, composition, and genetic origin to a substance already in the food supply, provided the existing substance, at the

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3 The Expert Panel noted that this feature is not unique to new food ingredients, but may also be a characteristic of food additives/GRAS substances.
concentration being considered, is regarded as acceptable by scientists and medical personnel with expertise in evaluating human health and food safety.

Substances that do not meet this standard, including cross-species substances, if proposed for use as a food ingredient or source of a food additive would therefore require safety testing with particular emphasis on those components that differed from their conventional counterpart.

- "Modified Foods": The Expert Panel also recognized that cases might exist were substances that are inherent components of foods might be increased to achieve levels reputed to have a health/nutritional benefit. In such cases, the distinctions between adulterated and unadulterated food, and foods and food additives would become blurred. As outlined by the FDA in its statement of policy on foods derived from new plant varieties (FDA, 1992), in such a scenario the Agency would consider the manipulated constituent as an additive covered by the FDCA (Sec. 409 of the FDCA and 21 CFR 170.30(f)). Consequently, a need would exist to bring the best available science to bear to determine whether that food not only continues to meet the standard of identity but that there is a reasonable certainty that the manipulation has not rendered that food harmful.

- "Cumulative Effects": The Expert Panel was aware of the need to address the potential for cumulative effects of new food additives as mandated in 21 CFR 170.18 (1994). "Food additives that cause similar or related pharmacological effects will be regarded as a class, and in the absence of evidence to the contrary, as having additive toxic effects and will be considered as related food additives." (21 CFR 170.18 [a], 1994). Provisions are then provided for setting tolerances for such related foods. "Where two or more chemicals in the same class are present in or on a food, the tolerance for the total of such additives shall be the same as that for the additive having the lowest numerical tolerance in this class, unless there are available methods that permit quantitative determination of the amount of each food additive present or unless it is shown that a higher tolerance is reasonably required for the combined additive to accomplish the physical or technical effect for which such combined additives are intended and that the higher tolerance will be safe." (21 CFR 170.18 [c], 1994).

In summary, the conclusions of the Expert Panel are intended to cover the safety evaluation of foods and food substances, inclusive terms intended to apply to anything that might be added to food. Many of these substances may be regulated as food additives, GRAS substances or by other means. A primary focus of this report is on macroingredients, i.e., substances consumed in a range of greater than 0.1% of the diet; however, wherever possible, the Expert Panel attempted to provide guidance for substances other than macronutrients that would require a new perspective to allow for the achievement of the same "reasonable certainty of no harm."

2. The choice: traditional or alternative approaches to testing?

As noted in Chapter I, the FAA stipulated that relevant factors to be considered in the safety evaluation of food ingredients include probable consumption of the additive and any substance formed because of the use of the additive, cumulative effects of the additive and pharmacologically related substances in the diet, and "safety factors" to allow the interpretation and extrapolation of animal experimental data (the Act and 21 CFR 170.3[i]). Toxicology studies typically provide the scientific basis for decisions rendered by the FDA on new food ingredients (FDA, 1982: Redbook I).

The FDA has acknowledged, in the revision of the Redbook and elsewhere, that the traditional model for safety evaluation as outlined in the Redbook may not apply to nontraditional types of food substances such as macro nutrient substitutes. As stated in Redbook II, "... it may not be feasible to calculate safety factors in the conventional way, that is, as a fraction of the highest oral dose that has no adverse effects in animals." (FDA, 1993). Because determination of an acceptable daily intake (ADI) by conventional means depends on the dose-response curve extending far beyond levels of anticipated normal consumption, a new approach to determining the ADI must be developed for nontraditional types of foods or food substances consumed at high concentrations in the diet.
The Expert Panel understood that a core issue in the decision to use the traditional and/or an alternative approach is the non-linear relationship between exposure and confidence in the traditional approach. It is apparent that once a critical exposure value of approximately 0.1% is exceeded, the utility of traditional testing protocols abruptly deteriorates. The Expert Panel's concerns about the appropriateness of traditional protocols for testing the safety of many novel food ingredients, e.g., substituted fats, is related to this and other aspects for the following other reasons.

1. The 0.1% concentration level was deemed "critical" because traditional animal testing protocols generally involve testing substances at a range of concentrations, the high end of which is much greater (100 to 1000-fold) than that intended for eventual use in human diets. This range is tested to define a dose-response relationship, to establish a no observable adverse effect level (NOAEL), to estimate an uncertainty factor, and to determine an ADI. If the proposed substance is intended for use at 0.1% in the diet, then a 100-fold elevation in animal diets would result in a diet concentration of 10%, that often would be sufficiently large to cause confounding dietary imbalances, the possibility of "pseudo-toxicity" (resulting from chronic changes in physiological homeostasis), occasional problems of diet rejection by test animals, and in general, a greatly decreased ability to accurately determine the intrinsic toxicity of the substance. Thus, as the proposed concentration of a new substance in the human diet increases above about 0.1%, traditional animal testing protocols become increasingly inoperative and unreliable.

Although the Expert Panel recommended the use of substance concentration as a logical basis for the choice between traditional (assuming that traditional protocols of a suitable nature are available for the substance in question when proposed for use at a low concentration) versus alternative approaches to safety evaluation of new food ingredients, it readily acknowledged that the critical concentration of 0.1% is an approximation and that a test procedure involving aspects of both traditional and alternative protocols occasionally may be most appropriate when evaluating substances at dietary concentrations at or close to 0.1%.

As a further caveat, the Expert Panel recognized that although 0.1% is a useful point of reference because of inability to interpret results of tests in animals subjected to doses at exaggerated doses relevant to the proposed conditions of use, there may be circumstances when the nature of the substance becomes an equally important factor. An example offered is the case of a new food or food substance that is similar to the substance that it is intended to replace in the food supply but does not meet the standard of identity. In this case, the level of consumption is one issue, but the potentially altered toxicity of the substance is of equal importance.

2. In some instances, a test animal that metabolizes and/or responds to the test substance in a manner analogous to that of humans simply cannot be found. For example, gastrointestinal intolerances or headaches experienced in humans cannot be evaluated in any animal. In these instances, use of animal models for estimating the risk of consuming a new substance, regardless of concentration in the diet, is of greatly reduced effectiveness.

3. The traditional model for safety evaluation of new food ingredients becomes dysfunctional in those situations where the new substance cannot be accurately assigned to one of the concern levels, i.e., the substance has a chemical composition that is too complex to be easily categorized.

Thus, a major issue faced by the FDA is how to respond to situations where there is no straightforward way to utilize animal models, in a traditional manner, to extrapolate potential risks to humans.

The Expert Panel viewed its tasks as (1) to specify those circumstances where the traditional approach for assessing the risk of new substances in the human diet is partially or totally inappropriate, and (2) to specify a process that will result in the identification of risk and an ADI (or some analogous measure of safe chronic intake) when the traditional approach involving animal models is inappropriate. The goal of any testing of new foods or food substances, whether by alternative, traditional, or some combination of approaches, would be the achievement of the standard of "reasonable certainty of no harm."
As a preamble to its recommendations, the Expert Panel established the following principles and criteria to be applied in its examination of the issues raised by new foods and food substances and its selection of strategies to meet the standard of "reasonable certainty of no harm."

B. PRINCIPLES

1. Risk versus safety

- The identification of a risk, while involving the judgement of scientists who are to some extent influenced by societal forces, nevertheless depends primarily on the application of scientific principles and procedures. Once the risk is identified, the decision about what is safe, i.e., risk management, can be made. The Expert Panel considered a decision about safety, including the use of uncertainty factors, as ultimately a policy decision made in the context of what level and kind of adversity is acceptable to society.

- Because the FDA asked for guidance on the scientific data required to make a safety decision, it became incumbent on the Expert Panel to have a working definition of what constitutes "risk" in the context of new foods and food substances. In the broad sense, the Expert Panel defined risk as the probability (in terms of frequency) of harm, i.e., an expected adverse effect over a defined period. In the context of the evaluation of new foods and food substances, the data that can be used to identify or predict an adverse effect, along with the associated uncertainty of these data are scientifically quantifiable.

The Expert Panel noted that inherent in its definition of risk is the implication that the effects of substances are presented in the context of whether the effect will occur, i.e., in the binary sense, yes or no. However, it is important to acknowledge that this interpretation and use of the term risk are only for convenience.

The Expert Panel also understood that the estimation of the risk (probability) that an adverse event will occur requires that one have an operational definition of the adverse event. For example, the investigation of the putative effects of a substance on the risk of the event "headache" might define "headache" as any pain above the neck for any magnitude, for any duration. Additionally, it might also be useful to define "severe headache" as any pain above the neck that the subject rates as "severe" or that lasts for more than two hours.

The Expert Panel recognized that other useful ways exist to quantify the effects of substances, such as relative risk (Hedges & Olkin, 1985; Rosenthal, 1991). This is particularly true in those cases involving continuous variables where mean differences, standardized mean differences, proportions of variance, binomial effect size displays and other expressions are not only available but may be more useful than risk that assumes a binary (yes/no) outcome (Hedges & Olkin, 1985; Kraemer & Andrews, 1982; Rosenthal, 1991). For purposes of exposition, the Expert Panel chose to use the word risk but, in general, the reader might substitute any legitimate quantitative measure of effect in its place.

- Ultimately, reliable management of risk, i.e., the safety decision, will necessitate the generation of a quantitative measure of the risk of an adverse effect. Generation of this quantitative measure traditionally has been based on the determination of a NOAEL and the use of an uncertainty factor. In the Expert Panel's view, the magnitude of the uncertainty factor must be based on sound experimental data. Although, a default uncertainty factor of 100 may be warranted in some instances, its use is not realistic in the case of food substances used at high concentrations in the diet. Consequently, the selection of appropriate uncertainty factors should be done on a case-by-case basis.

2. Characterization of adverse effects

An essential step in estimating the safety of a given food substance is extrapolation of the risk of an adverse event documented in animals or humans to humans under specified conditions of use. A fundamental element of this
decision is the definition of an adverse effect. The EPA defines an adverse effect as "a biochemical change, functional impairment, or pathological lesion that either singly or in combination adversely affects the performance of the whole organism or reduces the organism's ability to respond to an additional environmental challenge" (Crump et al., 1995). Although the Expert Panel agrees with the scope of effects considered in this definition, further detail is deemed necessary to provide what is considered to be a valid working definition of “adverse effect” within the context of food safety. The following is the Expert Panel's perspective on what constitutes an adverse effect in the context of the safety evaluation of new foods or food substances intended for use in the diets of humans:

An **adverse effect** in humans occurs when ingestion of a substance causes an effect, (i.e., a biochemical change, functional impairment, or pathological lesion), that either directly or indirectly adversely affects performance or reduces one's ability to respond to an additional environmental challenge.

To put this definition in perspective and within the context of safety evaluation of new substances to be included in the food supply, an additional question must be answered. When is an adverse effect sufficiently serious so that a new food or food substance fails to meet the standard of “reasonable certainty of no harm”? The Expert Panel provided the following criterion to address this question:

When an adverse effect caused by the substance at a specified exposure exceeds the frequency and severity that has been established by scientists and medical experts with expertise in evaluating human health and food safety, as common and acceptable in the general population and in relevant sub-groups thereof, then the new food or food substance exceeds the threshold exposure for harm, i.e., it fails to meet the standard of “reasonable certainty of no harm.”

Implicit in the Expert Panel's definition of adverse effect is the acceptability of trivial adverse effects. In its definition of adverse effects, i.e., the effects that the new compound produces under proposed conditions of use, the Panel acknowledged that effects may occur but that historically, the community has recognized the extent and nature of the effect as being trivial and generally regarded from a clinical perspective as being acceptable. However, the Expert Panel offered the following caution.

In cases where experiments involve comparison of the proposed substance's effects with those of a substance that is similar in nature, and which occurs naturally in the food supply, e.g., comparison between chemically modified hydrocolloid and a natural fiber, projected exposure becomes a critical factor in interpreting the results. Experiments of this kind inevitably lead to interpretations based on the assumption that the naturally occurring control substance has effects that are "common and acceptable" in the general population, as well as relevant population subgroups. As demonstrated in the following case study in which ringing in the ear or tinnitus is the suspected adverse effect, this assumption must be examined with care. One reason for selecting tinnitus as the hypothetical adverse effect is that a suitable animal model is not available, thereby necessitating trials in humans.

**Case study:**

Macroingredient, MI, is proposed as a new food additive. MI is known to cause increased incidence of tinnitus when used at high concentrations, and its functional properties are similar to those of substance C, which occurs naturally in many foods at substantial concentrations. C is therefore selected as a “control” substance for assessing the safety of MI. Assume the following is known about the effects of C on tinnitus:
Table 3-1. Effects of substance C on tinnitus.

<table>
<thead>
<tr>
<th>Exposure (eaters only)</th>
<th>Incidence (% of population)</th>
<th>Tinnitus Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentile</td>
<td>grams/day</td>
<td>10^5</td>
</tr>
<tr>
<td>50th</td>
<td>2</td>
<td>10^4</td>
</tr>
<tr>
<td>90th</td>
<td>4</td>
<td>10^3</td>
</tr>
<tr>
<td>99th</td>
<td>8</td>
<td>10^2</td>
</tr>
</tbody>
</table>

Assume that the effects of MI on tinnitus are the same as those of C at any given level of exposure. At the three levels of exposure, what might be an acceptable judgement regarding "reasonable certainty of no harm?"

- If MI is proposed at a 50th percentile maximum exposure of 2 grams/day a positive judgement would be justified.
- If MI is proposed at a 90th percentile maximum exposure of 4 grams/day a positive judgement would be questionable;
- If MI is proposed at a 99th percentile maximum exposure of 8 grams/day a positive judgement would not be justifiable.

The principle demonstrated by this case study is that judgements about whether adverse effects of naturally occurring components of human diets are or are not "common and acceptable" must account for the level of exposure in humans. This principle is applicable in cases where substantial equivalence is proposed as a criterion for safety testing and/or acceptability. For example, in the 99th percentile example, the establishment of substantial equivalence to a conventional food or food substance would clearly not be an acceptable standard for affirming a "reasonable certainty of no harm."

The Expert Panel emphasized that inherent in its definition of an adverse effect and the decision about what constitutes an adverse effect associated with a given substance under defined conditions of use is the understanding that all observed effects have been adequately evaluated.

3. Issues in experimental design: selection of controls

As seen in the previous example, the use of particular control substances and the subsequent interpretation of data from such comparisons are important considerations in the evaluative process. Implicit in the "degree or persistence of adverseness that has been established by medical experts as normal in the general population" is the issue of what constitutes a reasonable standard for comparison or "control" to establish whether an effect occurs and is harmful.

- In an experimental setting, the choice of a control sample is inextricably linked to the question one is asking regarding the substance, i.e., what types of adverse effects are of interest? Thus, the selection of a proper control sample depends on the attribute under study. The choice of what level/type of attribute is of interest and considered "adverse", as well as the adequacy of the uncertainty factor applied to the NOAEL generated from such experiments to provide an acceptable margin of safety, though based on sound scientific principles and data, are ultimately social/policy decisions. Several examples of study objectives and associated control sample types exist; among them are:
"Zero-tolerance" - This represents an absolute standard of no adverse effect. In this instance, the control samples typically would be animals or humans that are consuming normal diets (no test substance). The requirement would be that the adverse effects of interest could be statistically no more prevalent or no more severe in the presence of the test substance than in its absence. The most common use of a zero tolerance standard is for testing substances to determine whether they are carcinogenic. Taken to its extreme, the Delaney Clause of the FDCA is the codification of the zero tolerance standard. The clause, which was included as part of the FAA to the FDCA in 1958 states, "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animals." (21 U.S.C. § 348[c][3][A][1994]). As written, this codicil does not imply relative risk of cancer, i.e., a comparison to another substance, rather it demands the absolute absence of cancer.

In most (but not all, e.g., cancer) cases, the Expert Panel viewed the zero-tolerance standard as not realistic in most instances involving testing for adverse effects from new foods or food substances. In fact, the codified use of uncertainty factors, by implication, affirms this conclusion.

Use of a control substance that is functionally similar to the test substance. In this instance, one might consider the test substance harmful only if it has effects that are meaningfully worse by some degree than a currently available control substance that is legally safe and is functionally similar to the test substance. For example, the dietary component being replaced (e.g., starch) would be a reasonable control substance for the test substance (e.g., a chemically modified starch).

Use of a control substance that is not functionally similar to the test substance. This scenario would only be considered when a functionally similar substance does not exist in the food supply. In this instance, one might consider the test substance harmful only if it has adverse effects that are meaningfully more severe than a currently used substance that is legally safe, is not functionally similar, but has the greatest similarity to the test substance of any substance existing in the food supply. For example, dietary fiber of some type might be a reasonable control substance for a nondigestible macronutrient substitute. A related issue to this scenario is the potential for additive effects from the addition of the new substance to the food supply containing substances with similar adverse effects as those being evaluated.

Use of multiple control samples. In some instances, it is desirable to use multiple control samples. The specific types are dictated by the experimental objectives.

A further discussion of these and related issues in experimental design and hypothesis testing can be found in Chapter IV and, in particular, Table 4-4. The experimental designs needed for these studies flow directly from well established scientific practices and principles. Nevertheless, the selection of what questions are of interest or what comparators can set the standard of "not adverse" is also influenced by social/policy decisions.

The Expert Panel recognized that the term "background noise" is used in the context of risk assessment. However, the Panel viewed the term as nebulous and potentially subject to misuse. For example, if a substance causes an effect, e.g., tinnitus, in 10% of the sample studied, that effect could be dismissed as equivalent to the "background noise" (assuming an incidence of 10% in the general population consuming a variety of foods). This dismissal could be made irrespective of how that effect is viewed by the medical scientific community, i.e., the extent to which it is viewed as adverse. However, if the 10% experiencing tinnitus in the trial normally did not experience tinnitus, then to dismiss the outcome as unimportant because it does not exceed the "background noise" in the general population would be inappropriate. In
general, the Expert Panel viewed the "background noise" as more a reflection of the variability in the general population than a standard for comparison.

Thus, to compare the effects of a new food substance to those that might occur in the general population consuming a variety of foods is useful to gain an appreciation for the risk, to put the risk into some context, and to give perspective; however, under no circumstances should such comparison be in and of itself justification for an added risk associated with a new ingredient or be sufficient grounds for a safety decision. For example, the general population may exhibit a distribution with respect to a given health attribute, such as bone density, frequency of tinnitus, or blood pressure, that should not be regarded as an acceptable standard. This emphasizes the need to select experimental control conditions that accurately represent acceptable and realistic standards of health.

4. Approaches to testing

The goal of the Panel was not to abolish the traditional approach to safety evaluation of new foods and food substances, but rather to adapt it and utilize appropriate elements (or add new ones wherever warranted) for the evaluation of these materials. In recognition of the strengths of the "traditional approach," the Panel acknowledged that the new model will be similar to the principles applied in the Redbook, but also will differ in emphasis and application. The Panel emphasized that irrespective of the approach used, either traditional or nontraditional, the selection of appropriate tests must be done on a case-by-case basis with due consideration of exposure estimates, source material, complexity, and process.

The Expert Panel recognized that its task was to provide advice on the type and amount of scientific data required to make a decision about the risk associated with the proposed use of new foods and food substances, in particular, those that require testing that might be classified as nontraditional. The Panel concluded that the scientific standards required to make a decision about the risk associated with the proposed use of a given new substance should be the same irrespective of the regulatory classification, e.g., a food additive, GRAS, or new food. The Expert Panel therefore offered the following tenets with regard to the evaluation of new foods and food substances:

- To establish recommendations for the types of testing required for the risk assessment of new foods and food substances, it is essential that the types of effects that constitute harm be specified as accurately as possible.

- The nature and extent of the testing conducted for a new substance must be commensurate with the predicted risks to humans under proposed conditions of use.

- Testing procedures selected for new foods and dietary components that because of their nature or proposed conditions of use, i.e., those that will appear at high concentrations in human diets, obviate or limit the traditional use of animal studies must include an increased emphasis on clinical trials in humans and decreased emphasis on traditional toxicological procedures.

For those substances of simple chemical composition derived from conventional sources by conventional methods and occurring at low concentrations in food e.g., < 0.1%, the approach recommended by the Expert Panel is consistent with principles outlined in the Redbook; however, details of implementation may differ in some instances.

The process by which decisions are made regarding testing of new foods and food substances is detailed in Chapter IV.

- The Panel understood that consistent with FDCA and current FDA practice its recommendations about risk assessment of new foods and food substances, apply both to their innate toxic potency and their conditions of use rather than the substances themselves. The ultimate regulatory decision is an approval
for use under defined conditions rather than a blanket approval for the substance. Recommendations about the science required for such decisions must be made within this context.

5. Quantitative and objective data synthesis

Throughout the process of risk assessment as proposed by the Expert Panel, a key supporting element will be effective strategies for compiling and interpreting relevant information. Each stage of the assessment must involve thorough searches of the extant literature. In fact, the first step at each stage of the safety evaluation process must be the provision of quantitative estimates of key parameters. These parameters include those characterizing the effects of the substances under conditions of use and the distribution of intake (exposure estimates). In many cases, the data relevant to estimating any one of these quantities will come from more than one study. In such cases, methods for synthesizing data from multiple sources will be required.

A standard approach to this synthesis has been the generation of an informal subjective review, the limitations of which have been described by Cooper & Rosenthal (1980). The Expert Panel, although recognizing the place for such review as part of the overall process, advocated an approach that has the following requirements:

- Comprehensiveness: The data synthesis and parameter estimation procedures should, to the extent possible, incorporate all of the relevant data meeting well-defined inclusion criteria. The Expert Panel was concerned that relying only on published literature has the potential for introducing bias (Dickersin, 1990; Dickersin & Berlin, 1992). Moreover, whenever possible, the Panel recommended the analysis of raw data rather than the use of summary statistics (Jeng et al., 1995). Methods available for the comprehensive location and retrieval of relevant information have been presented (Cooper, 1989; Rosenthal, 1994; White, 1994). The Expert Panel recommended that all methods used to retrieve information be explicitly stated in the presentation of the evaluation process.

- Objectivity: The procedures for collecting, summarizing, and drawing conclusions from the data during each stage of the risk assessment process must be in accord with the most rigorous standards and must be described clearly. This will help assure the accuracy of the conclusions and the credibility of the process in the eyes of the public, and will allow for replication when needed.

- Quantitateness: The Expert Panel recommended that data manipulations be quantitative whenever feasible. For example, in reviewing available data from multiple sources (e.g., data on humans or dose-response data from animals) meta-analyses can be appropriately applied (Berlin et al., 1993; Greenland & Longnecker, 1992).

Quantitative synthesis of the data contributes in an important way to the objectivity of the process. The quantitative approach also allows clear and precise statements of risks and anticipated effects to be made in a way that cannot be matched by qualitative statements.

- Methodological Rigor: As with any scientific endeavor, the quality of the results depends in large part on the quality of the methods used. A detailed exposition of all of the components of an adequate data manipulation cannot be provided here; however, the Expert Panel refers the reader to reviews by Cooper & Hedges (1994) and Hedges & Olkin (1985) that reflect the standards and practices widely accepted by the scientific community.
IV. APPLICATION OF ALTERNATIVE APPROACHES TO SAFETY EVALUATION OF NEW FOODS AND FOOD SUBSTANCES

A. FRAMEWORK FOR ANALYSIS

In its deliberations, the Panel sought a framework that could be used to apply the concepts and testing approaches to be recommended in its report, and concluded that the scientific component of safety evaluation is, in reality, a risk assessment. As defined by the National Academy of Sciences (NAS), risk assessment in humans is "the evaluation of scientific information on the hazardous properties of environmental agents and on the extent of human exposure to those agents. The product of the evaluation is a statement regarding the probability that populations so exposed will be harmed and to what degree. The probability may be expressed quantitatively or in relatively qualitative ways" (NRC, 1993, p.25).

The members of the Expert Panel agreed that in order to meet the standard of "reasonable certainty of no harm" a systematic approach to the safety evaluation of new foods and food substances was needed. They concluded that the NAS definition of risk assessment is consistent with the goals of the scientific component of the safety evaluation of new foods and food substances because it is presumed to encompass the core ingredients necessary for that evaluation, i.e., hazard identification, exposure estimates, and the generation of quantifiable reflection of the risk from exposure to a given substance. Once accomplished this estimate of risk can be used by the risk managers, those whose task it is to synthesize all the required information into a safety decision. The flow of information that must be collected and used to support a safety decision is represented in Figure 4-1.

The Expert Panel's adaptation of the framework outlined by the NAS (NRC, 1982, 1994) for risk assessment for the process of safety evaluation of new foods and food substances contains the following four elements:

1) Exposure assessment: estimation of the extent of human exposure to the substance under specified conditions of use.

2) Hazard identification: assessment of whether a particular substance is or is not causally linked to particular health effects.

3) Dose-response assessment: determination of the relationship between the magnitude of exposure to the substance and the probability of occurrence of the adverse health effect(s) in question.

4) Risk characterization: description of the nature and often the magnitude of human risk associated with the substance under specified conditions of use, including attendant uncertainty. According to the NAS, risk characterization, "...combines the assessment of exposure and response under various exposure conditions to estimate the probability of specific harm to an exposed individual or population."

B. PROPOSED EVALUATION PROCEDURES

Although the Expert Panel viewed the conceptual framework provided by the NAS approach as useful, it also concluded that there was a need to adapt this approach to the unique questions raised by the advent of the new foods and food substances to be addressed in this report. Prior to the implementation of a risk assessment, questions must be asked on a case-by-case basis to determine the necessity for and best types of testing to use. The following is a decision tree for testing of new foods or food substances, and a detailed description of how each step is applied to the risk assessment of these materials.
Figure 4.1. Stages in risk assessment

The Agent
Hazard Identification
- Enumeration and description of adverse effects?

Dose-Response Assessment
- How do severity, incidence of adverse effects change with dose?

Population(s) Exposed to the Agent
Exposure Assessment
- What dose, duration?
- How is dose distributed?

Risk Characterization
What is the likelihood that exposed populations will experience adverse effects?

How certain?

Adapted from Rodricks, 1996
1. **An alternative approach for risk assessment of new foods and food substances**

   The difference between the Alternative Approach proposed by the Expert Panel and the current approach, as outlined in the Redbook, is the elimination of the assignment of concern levels (CL). As currently outlined, the assignment of a CL cannot accommodate for complexity of new foods and food substances, the source material, or the novelty of the process. The assignment of a CL will be replaced by the Characterization phase which in turn will be followed by a risk assessment.

   a. **Step 1: Characterization**

      This step will involve the complete characterization of the physical properties of the new materials with particular attention paid to the information required to support (or not) a decision of substantial equivalence and to classify the materials for the purpose of deciding on the need and the appropriate approach to be used for testing as outlined in Table 4-1. The elements of that data set will include:

      - chemical nature: single entity, multiple complex\(^1\), food
      - source material(s)
      - process
      - manufacturer’s exposure estimate under proposed conditions of use

   **Step 2: Risk Assessment**

   This phase consists of the following elements:

   - **Exposure estimation**: The generation of a conservative estimate of 99\textsuperscript{th} percentile (or the highest percentile that can be reasonably estimated with good accuracy) of eaters, potential problems for subgroups, etc.

   - **Hazard Identification**: The determination of tests to be used will be based on Step 1 and will consist of several options: the Redbook approach (traditional animal toxicological testing), modified Redbook approach plus additional animal tests, or modified Redbook approach plus increased emphasis on clinical trials in humans (animal testing to identify potential effects but not to quantify dose for humans). The general categories of substances and criteria for selection of related testing approaches are summarized in Table 4-1.

   - **Dose-Response**: establishment of dose-response curve and generation of NOAEL will be accomplished on a case-by-case basis and will be dependent on the nature of the substances, i.e., exposure, complexity, source, and process.

   - **Risk characterization**: will be contingent on the nature of the risk as identified in the hazard identification phase and the exposure scenarios, i.e., who are projected eaters, potential high-risk subgroups.

   The following sections include expanded discussions of the elements of the Alternative Approach.

2. **The application of risk assessment to new foods and food substances**

   The Expert Panel recommended that the sequence of steps for risk assessment used in the Alternative Approach be changed from that recommended by the NAS (NRC, 1982) to make the process more compatible with the unique needs

\(^1\) The Expert Panel defined complex substances as those that are chemically heterogeneous, and either do not pass the test of substantial equivalence or provide an obvious frame of reference for such comparisons as described in the structure categorization process outlined in Redbook (FDA, 1982).
related to new food and food substances, particularly those used at high concentrations in the diet. Because of the increased emphasis on clinical trials, exposure estimation assumes a position of even greater importance in the Alternative Approach than in the Redbook. Consequently, early information on human exposure to the substance will enable the selection of dose ranges for these clinical trials that are much more realistic than would otherwise be possible. This will, in turn, facilitate development of an accurate dose-response relationship.

a. Exposure assessment:

In the premarket phase of the risk assessment, the endpoint of the process of exposure estimation is the generation of an estimated daily intake (EDI). According to Rulis (1991), the EDI "...is the exposure level that is consistent with what the FD & C Act refers to as the level of 'probable consumption' of the additive. Such an estimate is often based upon conservative assumptions in order to properly take into consideration that certain subgroups of the population will ingest more (possibly much more) of the additive than others."

As stated in the Redbook (FDA, 1982), "Initial assignment of an additive to a level of concern relates to general considerations of safety for the entire population. For this purpose, the agency has chosen to use estimates of per capita exposure based on the total poundage of a substance added annually to the U.S. food supply." The Expert Panel viewed this approach as limited and potentially misleading due to (1) the potential for underestimating the exposure for eaters (consequent to the dilution effect of including non-eaters in the estimate), (2) the potential for overestimating exposure for individuals who would not consume products containing the new substance, (3) the unreliability of data supplied voluntarily by manufacturers, and (4) the uncertainty of whether the amount of the substance added to the food supply is, in fact, consumed.

The Panel noted several other points about exposure estimation that warrant mention. In Redbook II (FDA, 1993), the FDA observed that its approach to exposure estimation is based on certain assumptions concerning intake patterns, market penetration, and substance concentrations that will "result in a conservative estimate of exposure." It is further stated that in the premarket phase, the estimations of "probable human exposure are based on food intake or food availability data obtained over relatively short time frames (one day to one year) and are used to represent chronic or "lifetime" exposure." FDA goes on to note that the 90th percentile is used to "represent probable exposure for a heavy consumer of a substance."

The Expert Panel's approach to exposure estimation included the following elements:

- The Panel recommended that the calculation of exposure estimates should occur in conjunction with (or perhaps prior to) the early stages of hazard identification because of its importance in the design and interpretation of studies during hazard identification and the generation of dose-response curves to be used to generate data for the risk characterization stage. The importance of exposure estimation in the hazard identification phase is consistent in principle with the approach to generation of CL outlined in the Redbook (FDA, 1982). However, rather than limiting its use to categorization for the purpose of applying a prescribed series of standard tests, additional emphasis in the alternative approach would be on: (1) prediction of adverse effects, e.g., identification of potential nutritional problems, and (2) identification of specific population subgroups suggested in the initial characterization phase and subsequently by the comprehensive characterization of the hazard identification phase.

- Exposure estimation and further identification of potential adverse effects must involve the following two components:
  
  - Estimation of the expected mean and some designated upper percentile of consumption for various subgroups of the population, e.g., age groups, ethnic groups, gender, as appropriate.
  
  - Evaluation of the potential to displace nutrients in the diet through changes in dietary patterns. Though not an exposure issue per se, techniques in exposure estimation along with the results of the
comprehensive characterization can generate information that could predict this potential adverse effect of exposure to the new substance.

- Estimates should relate to eaters only whenever possible. Assuming that not all persons in the population will consume foods containing the proposed substance, then exposure estimates calculated on a per capita basis will not accurately represent what eaters consume. Use of the per capita approach will result in exposure estimates for eaters that are usually too low. This inaccuracy could potentially be large and lead to a significant underestimation of risk particularly if eaters comprise a small fraction of the population. An erroneous estimation of this magnitude will also result in faulty data to be used in the design of doses for clinical trials, which would hamper efforts to generate an accurate dose-response relationship.

- Exposure estimates should be derived for both the general population and for those population subgroups considered most sensitive to the test substance.

- When calculating exposure levels, it is useful to distinguish among exposure levels over differing durations. Depending on the (presumed) effects of the substance under study, one may be interested in either acute (e.g., daily) or chronic (e.g., average over several months or more) exposure. The Expert Panel recognized that these temporal considerations will exist over a continuum. The upper percentiles of the chronic intake distribution will generally be lower than the corresponding percentiles from the acute intake distribution and the converse is true for lower percentiles.

- The choice of which distribution to estimate (and more than one may be selected) will depend on the substance under study and its presumed effects. For example, if the substance under consideration was believed to have acute effects on gastrointestinal function or heart rate, then estimating the distribution of daily intake would be desirable. In contrast, if a new fat was introduced that might induce fatty deposits in the arteries leading to heart disease, then chronic exposure would be of greater interest.

- Whether the basis of concern is excessive acute and/or chronic intake of a test substance, the estimate should be constructed to err on the high side, and mean and a high (e.g., 99th percentile, if available) estimate should be provided.

- If the basis of concern is inadequate intake of a test substance or inadequate intake of some other essential dietary component whose utilization is inhibited by the test substance, then the estimate should be constructed to err on the low side, and mean and low (1st percentile) estimates should be provided.

- Eating occasions at home and away from home should be included in the estimate.

- If the substance is not “interchangeable” with an existing dietary component of similar chemical and functional properties, this fact should be noted along with the observation that introduction of the new substance is likely to increase total consumption of this chemical class. Thus, an exposure estimate(s) should be derived for the new substance, as well as an estimate(s) of total exposure to all members of this chemical class.

- If the substance is “interchangeable” with an existing dietary component of similar chemical and functional properties, this fact should be noted along with the observation that introduction of the new substance is unlikely to increase total consumption of this chemical class. In this instance, an exposure estimate(s) for the new substance will suffice.

- In some instances, the substance of interest may enter the body by means other than food and beverages (e.g., air, dietary supplements, pharmaceuticals, cosmetics) and these possibilities should be considered when deriving exposure estimates.
Table 4-1. Categories and criteria for testing in hazard identification phase.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>EXPOSURE</th>
<th>STRUCTURE</th>
<th>SOURCE/PROCESS</th>
<th>TESTING</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt;0.1%</td>
<td>Single chemical entity</td>
<td>not novel</td>
<td>Redbook approach: utilizing standard animal toxicological testing</td>
<td>This category contains many of the substances evaluated with the traditional approach as conceptualized in the Redbook (FDA, 1982)</td>
</tr>
<tr>
<td>B</td>
<td>&lt;0.1%</td>
<td>Single chemical entity</td>
<td>novel</td>
<td>Establishment of substantial equivalence where relevant; Redbook approach: utilizing standard animal toxicological testing plus additional tests as needed.</td>
<td>Animal testing is probably appropriate for identification of standard adverse effects. However, there would be a need for additional new types of testing, e.g., immune response for potential food allergies/sensitivity, and an increased reliance on clinical testing in humans to account for effects that might be untestable or undetectable in animal studies.</td>
</tr>
</tbody>
</table>
| C        | >0.1%    | Single chemical entity     | not novel      | Redbook approach: utilizing standard animal toxicological testing, particularly with regard to potential chronic effects, plus additional tests and increased reliance on clinical trials in humans and pre- and postmarket surveillance. | Animal testing would be appropriate for identification of potential adverse effects, but not for establishment of NOAEL. Consequently, ADI cannot be determined by conventional means. Recommendation to the FDA of an Acceptable Chronic Exposure (ACE) based on third party evaluation of test data. Other issues:  
- Heavy reliance on clinical trials and initial characterization (for prediction of potential acute and chronic effects).  
- Identification of reliable endpoints for both acute and chronic effects. With regard to the latter, animal testing may still serve as an important component along with postmarket surveillance.  
- Increased attention must be given to nutritional consequences of ingestion of the new substance at high concentrations in the diet  
- Increased attention must be given to the consequences of increased exposure to the class of chemical substances to which the new substance belongs, i.e., additive effects. |
<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>EXPOSURE</th>
<th>STRUCTURE</th>
<th>SOURCE/PROCESS</th>
<th>TESTING</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>&lt;0.1%</td>
<td>Complex chemical entity</td>
<td>not novel</td>
<td>Establishment of substantial equivalence where relevant types of testing required must be determined on a case-by-case basis in consultation with FDA. The NOAEL approach can be used for both the parent compound and subcomponents/metabolites. Some clinical testing in humans, e.g., allergenicity tests, will be necessary, again chosen in consultation with FDA.</td>
<td>Standard approach to assigning Concern Level as outlined in Redbook is not applicable. Animal testing is appropriate however, for both the parent compound and subcomponents/metabolites, the types will be contingent on the information garnered in Step 1, the characterization phase. Particular attention must be paid to effects such as allergenicity that might be difficult to examine in animal models.</td>
</tr>
<tr>
<td>E</td>
<td>&gt;0.1%</td>
<td>Complex chemical entity</td>
<td>novel/not novel</td>
<td>Same as category D. In addition, types of testing required must be determined on a case-by-case basis in consultation with FDA. Increased attention must be given to nutritional consequences of increased exposure to the class of substances to which the new substance belongs. Extensive clinical testing in humans will be required. New tests with or without animals will be required, however the NOAEL/ADI approach cannot be used for the parent compound. Recommendation to FDA of an ACI value should be based on third party evaluation of test data.</td>
<td>Increased reliance on Step 1 characterization phase to identify potential adverse effects. Concerns are how to generate the ACI value (in lieu of an ADI), appropriate identification and application of uncertainty factors, and identification of appropriate tests or markers for effects that are untestable and/or undetectable in animals. Chronic effects may be identified and examined in animal testing; however there will be an increased reliance on postmarket surveillance.</td>
</tr>
</tbody>
</table>
If the substance's effects on specific populations groups (e.g., based on age, race, gender, height, weight, dietary intolerances, reproductive status, health status, socioeconomic status) are potentially important (as predicted by the hazard identification phase), then exposure estimates for these groups should be provided, in addition to those for the general population.

The Expert Panel recommended that selection of doses for dose-response estimation should, whenever possible, be multiples of the estimated human exposure.

The Expert Panel did not consider a critical review of available methodologies for exposure estimation to be within its purview. For a detailed description of the techniques and methods available for exposure estimation the Panel refers the reader to the following two reports:


b. Hazard identification

The goal of hazard identification is to identify the type and range of adverse effects associated with a given food or food substance. The following is a description of the process by which one might identify specific risks of harm or adverse effects for a specific substance. In conjunction with the information garnered from the exposure estimation, the other core element contributing to the determination of the type and dose ranges to be used to test for adverse effects will be the comprehensive characterization of the chemical and physical properties of a new food or food substance. The key difference between the approach proposed by the Expert Panel and that suggested in the Redbook(s) is that rather than basing the testing solely on exposure and structure, the Alternative Approach utilizes a case-by-case analysis that accounts for such additional factors as complexity (single entity versus complex mixtures or whole foods), novel source materials, and novelty of production method in the determination of appropriate testing.

In the case of substances with potential use at greater than 0.1% of the diet, the differences between the traditional and Alternative Approach to hazard identification are related to an increased emphasis on nutrition-related tests necessitated by caloric dilution and potential interference with absorption and utilization of other essential nutrients. Because of the complexities of these interactions, animal studies may be ineffective for defining a dose-response relationship. Although it is possible to identify hazards qualitatively, it is not always possible to quantify such effects in animal studies. Consequently, the Alternative Approach will require an increased reliance on clinical trials in humans, particularly with regard to potential acute effects.

In the case of those foods or food substances of complex nature, derived from new source materials, and/or those that result from the use of new methods of production, the Expert Panel agreed with many of the recommendations outlined by other organizations, e.g., the U.K. reports on novel foods (Advisory Committee on the Assessment of Novel Foods and Processes; ACNFP; 1991, 1994) and the Commission of the European Communities (1989, 1996)(see Chapter II, Table 2-1). The characterization process in the Alternative Approach is specifically intended to provide data to establish whether the new products meet the standard of substantial equivalence. For those products that do not meet that standard, a particular concern is the potential allergenicity of the new products. As this is a component of testing that has not been previously emphasized in the traditional approach as outlined in the Redbook (FDA, 1982) and because allergenicity is not easily identified in animal models, the Panel emphasized the importance of the characterization phases and subsequent clinical studies in the identification of the effect. The recent compendium on the allergenicity of foods produced by biotechnology by Metcalfe et al. (1996) contains useful background on current testing approaches and issues to be considered in the examination of this important issue.
The Expert Panel has concluded that the model proposed by Munro et al. (1996b) offers a sound approach for the identification of potential adverse effects from new foods and food substances. The essential components of this approach include:

- **Thorough characterization of the physical and chemical properties of the substance:** An important component of this step is the comprehensive literature search designed to uncover all research relevant to the new ingredient. This review must be exhaustive, covering standard sources of scientific information (books, journals, government publications), as well as other reputable sources of scientific information (research reports, theses, data generated in industrial laboratories, etc.). Primary sources of data should be used consistently. Analysis of the collected data must be done by objective experts and meta-analysis should be considered for data from multiple sources.

Table 4-2 contains an adaptation of the listing by Munro et al. (1996b) of types of characterizations that might be considered:

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Physicochemical Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chemical reactivity</td>
<td>• Physical state</td>
</tr>
<tr>
<td>• Functional group(s)</td>
<td>• Melting/boiling point</td>
</tr>
<tr>
<td>• Stereochemical configuration</td>
<td>• Molecular weight</td>
</tr>
<tr>
<td>• Comparative structure-activity relationship</td>
<td>• Particle size</td>
</tr>
<tr>
<td></td>
<td>• Solubility</td>
</tr>
<tr>
<td></td>
<td>• Octanol/water partition coefficient ($k_{ow}$)</td>
</tr>
<tr>
<td></td>
<td>• Ionization constant</td>
</tr>
<tr>
<td></td>
<td>• Chelating potential</td>
</tr>
</tbody>
</table>

adapted from Munro et al. (1996b)

As outlined by Munro et al. (1996b), the characterization of the physical and chemical properties of the new ingredients can provide a solid basis from which to predict the nature of biological effects that might be anticipated. Table 4-2 provides some guidance on the nature of the characterization required. More specifically, if thorough analysis of the chemical and physical properties along with an estimation of exposure in humans is carried out, many of the expected nutritional or physiological effects may be predicted beforehand. For example:

- The chemical and stereochemical configurations of a new food substance provide information relevant to its potential for absorption or for interference with the digestion and absorption of essential nutrients.

- The identification of the various functional groups of the new substance allows the chemical reactivity and potential for interactions with dietary constituents to be predicted.

- The description of the physicochemical properties including solubility, partition coefficient, and ionization constant can provide insight into the potential for absorption, subsequent distribution, and elimination.

- Other information regarding the physical state, solvent, and chelating properties of the substance provides insight into potential effects on or interference with the absorption of dietary components. For example, knowledge of the solvent properties of an unabsorbed fat or fatty acid hydrolysis
product can provide some indication about potential interactions with other fat-soluble substances, e.g. vitamins A, D, E, or K. Consideration of chelation properties will give an indication of potential interference with mineral absorption.

- **Metabolic characterization**: Using information garnered from the chemical characterization often enables the prediction of many of the metabolic and physiologic effects of new food substances. This would be analogous to the A.D.M.E, test selection process described in the Redbook (FDA, 1982). Initial approaches to these issues should involve an assessment of the fate of the material in appropriate in vitro systems. For lipid-based materials, the products of digestion catalyzed by lipases, under conditions simulating those prevailing in humans, provide a means of assessing the extent and type of degradation expected. Modified starches and polyols may be exposed to appropriate intestinal enzymes to evaluate the extent of hydrolysis that might be expected to occur. The action of intestinal microflora obtained from intestinal or fecal contents provides a means of assessing the potential for fermentation. From this series of studies, the degradation products can be identified and quantified, providing information on what can be expected to occur metabolically in humans.

- **Animal studies**: Although the advent of new types of foods and food ingredients will force the reassessment of their use, particularly in the dose-response phase of the risk assessment, animal studies must still play a large role in the hazard identification phase of the safety evaluation of these new substances. Harris (1997) summarized the three main advantages of animal testing as speed, cost, and control, and delineated many of the specific reasons, some intuitive and some not, justifying the use of animal models in the hazard identification phase of the safety evaluation process. In addition to obvious advantages of animal studies such as uniformity and availability of subjects and more rapid experimental turnover, other advantages of animal (versus human) studies include:

  - the ability to evaluate potential mechanisms of adverse effects more effectively;
  - the ability to study the effects of sub-components and/or metabolites of the parent compound;
  - the ability to perform long-term studies to assess potential chronic effects of new foods and food substances, a particular advantage in the premarket phase;
  - the ability to manipulate a single dietary component while controlling all other variables;
  - the ability to take invasive and often fatal end-point measures;
  - avoidance of errors in estimation associated with human trials, such as those associated with the use of dietary intake assessment methods, e.g., dietary recall, food diaries, food frequency questionnaires;
  - lack of problems associated with compliance and attrition;
  - no deviations from experimental protocol;
  - the ability to make often extreme dietary manipulations to assess the potential for creation of nutritional deficits or imbalances; and
  - the ability to assess potential responses in some sub-populations that may be at increased risk such as infants and/or the elderly.
In vivo studies should be designed with the objective of confirming predictions from the analysis of chemical and physical properties and the results of in vitro studies. They also provide an opportunity to extend the research program to evaluate potential physiological and metabolic effects that may occur.

A critical step in the design of in vivo studies is the selection of appropriate species. Harris (1997) asserted that digestive processes, metabolism (particularly of relevant nutrients), and feedback control of regulatory mechanisms of the selected animal models should be analogous to those in humans. For example, the well-known metabolic differences associated with using the rat for toxicology studies with polyols and modified starches dictate that the results of any studies of these or similar substances conducted in this species need to be interpreted with caution. In light of these considerations, it would be useful to conduct preliminary investigations using the rat; however, studies in other laboratory species, particularly monogastric species such as pigs or nonhuman primates, and clinical investigations in humans would be more desirable.

Initial in vivo studies should involve single-dose administration to confirm predictions from previous studies. These studies should be designed to evaluate a series of parameters including, as appropriate:

- bowel transit time, which will affect nutrient digestion and absorption;
- effects on vitamin, mineral and macronutrient absorption, digestion, and subsequent utilization;
- effect on fecal composition to evaluate nutrient loss and gastrointestinal microflora;
- effects on serum chemistry and urine composition; and
- metabolic studies to confirm in vitro predictions, and the deposition and fate of the test substance.

Repeated dose studies (28-day studies) should also be conducted by incorporating the material into the diet of animals, taking into consideration the anticipated level of human exposure but without compromising the nutritional state of the test animals. In addition to the parameters listed in Table 4-3, investigators conducting repeated-dose studies should consider the following issues:

- the need to evaluate the substance's metabolism by colonic bacterial metabolism;
- an evaluation of hepatic and renal function and any potential impact on nutrient utilization beyond what was included in the single-dose studies;
- a design that allows for precise measurement of food intake, weight gain, organ weights, carcass composition, and, as required, energy utilization;
- thorough histological examinations of all organs including bone, with particular emphasis on the histology of the gastrointestinal tract; and
- if warranted, based on the chemical and physical characteristics and the metabolic effects of the test substance, conduct an investigation of potential interactions, e.g., changes in absorption and metabolism, between the test substance and drugs commonly used in humans.

The parameters to be evaluated in single and repeated dose studies in animals are summarized in the following table:
### Table 4-3. Assessment parameters\(^2\) for animal studies relevant to the safety assessment of new food ingredients.

<table>
<thead>
<tr>
<th>Category</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-dose studies</strong></td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>(^{14})C label distribution, Metabolite identification, Clearance</td>
</tr>
<tr>
<td>Physiology</td>
<td>GI function, Transit time, Behavior, Fecal/urine composition</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Interaction with dietary nutrients</td>
</tr>
<tr>
<td><strong>Repeat-dose studies</strong></td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>(^{14})C label distribution, Induction of metabolism</td>
</tr>
<tr>
<td>Physiology</td>
<td>GI function, Organ function, Endocrine effects, Neurotoxicity/neurophysiology</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Nutrient balance studies, Tissue stores</td>
</tr>
<tr>
<td>Animal health</td>
<td>Food intake/weight gain, Behavior, Organ weight, Histopathology, Serum chemistry, Hematology</td>
</tr>
</tbody>
</table>

**Human studies:** As noted previously, particularly in the classification scheme presented in Table 4-1, the advent of new foods and food substances derived from new source materials, processes, or proposed for use at high levels of consumption requires an increased emphasis on and use of clinical trials in humans\(^3\). For a given substance, the conduct of such studies will be contingent on the demonstration in the in vivo animal studies of a reasonable certainty of no harm to humans with regard to obvious health risks. The purpose of clinical trials in humans would be to confirm the absence of adverse metabolic and physiological effects, particularly those that would be difficult to detect in animals, and to assess the relevance of experimental findings in animals to conditions of use in humans. Several factors should be considered in the design of human trials:

\(^2\) Although recognizing the importance of these parameters, the Expert Panel concluded that it was beyond the scope of this report to provide a critical review and evaluation of the most reliable methodologies for the assessment of each of these variables.

\(^3\) The Expert Panel recognized that because of logistical reasons, e.g., subject availability/compliance, resource limitations, etc., the focus of clinical studies in humans would be on acute effects, thereby necessitating the continued use of long-term animal studies. The nature, i.e., parent compound versus sub-component/metabolite, and dose of the materials to be tested in such studies would be based on the characterization phase and an interaction between the petitioner and FDA scientific staff.
- Because of the well-recognized impact of bolus feeding of nonnutritive substance on intestinal transit time and gastrointestinal function, human studies must involve incorporation of the test material into food. An acceptable procedure has been described in Health Canada (1994b).

- The test material should be consumed via the intended food matrices, employing the consumption pattern and daily frequency typically associated with the elected food types.

- The dose levels should span the range of the projected mean and upper level of intake, i.e., 90th percentile or higher where possible, calculated from proposed use patterns.

Initial studies usually involve a single day of administration in typical foods while long-term studies involve consumption of foods containing the test material as it is intended to be used over a period of several days or weeks. The physiological and metabolic effects observed, if any, in the animal studies should be carefully evaluated in humans. In addition, clinical parameters should be evaluated as itemized in Table 4-4. Reports of effects on gastrointestinal function, stool consistency, and nutrient balance should be carefully tabulated and analyzed, as such effects, although possibly not considered medically significant, i.e., adverse enough to warrant disapproval, would have important implications for labeling requirements.

In addition to the above considerations, the Expert Panel recognized that generally accepted principles exist for the conduct of clinical trials in humans (Meinart & Tonascia, 1986; Piantadosi, 1997; Pocock, 1983). Among these fundamental principles are:

- Randomization: Random assignment to treatment groups must be performed in a systematic and coordinated manner.

- Placebo control: Whenever possible, the control group should receive a placebo that is identical in appearance and taste to the substance being tested. However, the Expert Panel recognized that with macroingredients this may not always be possible.

- Double-Blind: Both the research subjects and the investigators must have no knowledge of the assignment of treatments to subjects until completion of the study.

- Cross-over designs whereby subjects can be used as their own control allow for both within- and between-group comparisons. The cross-over period must include a wash-out period of appropriate length to allow for objective comparison of treatment and placebo conditions.

- Statistical analyses: in general, the most powerful statistical technique that yields a valid test of the hypothesis should be used. In that context, many experts in the design of clinical trials believe that an “intent-to-treat analysis” is the most appropriate type of primary analysis.

- Statistical power: the study should be designed to have a high probability (power) of detecting the smallest level of a putative effect that is of interest. Many factors can affect statistical power including the number of subjects studied, and the precision of the measurements.

- Study duration: the study duration should be selected so that a) there is sufficient duration of exposure to allow for a putative effect to occur, and b) sufficient statistical power is achieved. Study duration should be justified a priori on this basis.

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4 An “intent-to-treat” analysis is defined as an analysis in which the independent variable is the condition to which subjects were randomly assigned regardless of the actual treatment they received and whether and when they dropped out of the study (Little & Yau, 1996)
Table 4-4. Clinical parameters relevant to the safety assessment of new foods and food substances.

<table>
<thead>
<tr>
<th>Category</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical observations</td>
<td>General health status (including specific emphasis on immune response, behavioral/cognitive function, neurological exam)</td>
</tr>
<tr>
<td></td>
<td>GI tolerance</td>
</tr>
<tr>
<td></td>
<td>Stool consistency</td>
</tr>
<tr>
<td>Clinical hematology and chemistry</td>
<td>Hematology</td>
</tr>
<tr>
<td></td>
<td>Serum chemistry</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Volume</td>
</tr>
<tr>
<td></td>
<td>Electrolytes</td>
</tr>
<tr>
<td></td>
<td>Tissue damage markers</td>
</tr>
<tr>
<td>Nutrient balance</td>
<td>Fecal/urine composition</td>
</tr>
<tr>
<td>Energy utilization</td>
<td>Fecal energy</td>
</tr>
<tr>
<td></td>
<td>Urinary energy</td>
</tr>
</tbody>
</table>

Selection of Controls:

A key issue in the design of studies involving animals or humans is the selection of appropriate control groups and/or substances. The Expert Panel previously identified several scenarios and associated issues to be considered when selecting controls. Although many of these issues will be addressed on a case-by-case basis, there are some general issues that apply irrespective of the type of substance being evaluated.

The most fundamental question driving the selection of controls is, "what is the null hypothesis of the study?" Recognizing that the process of hazard identification is a multi-step process involving several different and not necessarily mutually exclusive hypotheses, the Panel identified the following options for core hypotheses:

- "Does the substance cause any effects?" (Zero tolerance): The issue is whether use of the substance in question increases the incidence of the effect beyond what would be expected without the substance.

- "Does the substance cause an effect that is different from that of the substance it might be replacing?" In this case, the obvious control would be substance being replaced. For example, if a non-caloric fat substitute is being tested then the fat or oil currently found in the foods would be the proper control.

- "Are there substances in the food supply, e.g., substance X, that are chemically different from the test substance and have different technical effects but cause similar physiological/metabolic effects? If so, does the test substance present a greater relative risk to the general population because of its character and potential exposure than substance X?" Here, the control group would receive

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5 The Panel noted that the term "controls" is often used interchangeably to describe control groups and control substances used for comparison. "Control groups" refers to the group of subjects that would serve as a standard of comparison for the event rate or level of dependent variable, whereas "control substance" refers to the materials (e.g., foods or food substances) that are given to the control group in place of the substance under study. The Panel considered that all studies designed to determine whether an effect occurs require the use of control groups; by contrast many, but not all, require control substances. Examples of control groups and/or substances are presented below in the context of overall study objectives or hypotheses to be tested.
substance X. For example, substance X might be a legume chosen as control substance for a new non-absorbable fat replacer.

"Is there a potential for an additive effect?" As noted previously a regulatory mandate exists regarding this issue [21 CFR 170.18 (1994)]. Here the control groups would receive those substances in the food supply that have similar effects, while the experimental groups would receive either a combination of control substances, i.e., conventional foods or food substances, and the proposed new food or food substance or the new substance only. Control substances could include foods, other substances, e.g., a fat substitute compared with other fat substitutes, or those substances in the food supply added for different technical effect but with similar physiological effects (e.g., a bulking agent and a nonabsorbable macronutrient substitute). This question assumes greater significance in the Alternative Approach particularly because there are no provisions for testing this hypothesis in the Redbook or its revisions.

Table 4-5 is a summary of the relationships among these questions, experimental design and subsequent interpretations of results for the generation of a safety decision.

In the case of a new food, produced for example as a result of genetic modification, the standard is, as discussed in Chapter III, substantial equivalence. As outlined by the FDA (FDA, 1992) and as implemented in the agency's decision regarding the "Flavr-Savr" tomato (Hattan, 1994), the question is "does this new food differ from the old food?" Here, the comparison would be the new food versus the old, again provided that the old food has no adverse effects in the general population.

In most cases involving new food substances with specific technical properties, as opposed to new types of foods, most of these questions will need to be addressed. The Panel concluded that the use of multiple controls offers the best and most efficient means of deriving useful scientific information.

c. Dose-response assessment

Once the risk(s) associated with a new food or food substance has been identified, it is necessary to generate a quantitative estimate of the impact of the risk in the context of the substance's use in the diet both acutely and as a result of chronic use. What is ultimately desired is an estimate of the safe exposure level, traditionally represented by an estimated acceptable daily intake or ADI. Because the goal of the risk assessment is a reflection of risk from both acute and chronic exposure, with an emphasis on the latter, the Expert Panel chose to use the term Acceptable Chronic Intake (ACI) to replace the traditional ADI. To achieve this estimate, one must first evaluate the dose-response data and determine, "...the highest exposure among all the available experimental studies at which no toxic effect was observed" (NRC, 1994). The obvious exception to this approach occurs when the goal is zero tolerance as for substances that may be carcinogenic. For all other cases, the highest level of exposure for which there is no effect is termed the no observable adverse effects level, NOAEL, and traditionally for substances such as food additives, it has been generated from data garnered in animal toxicology studies.

For substances that are proposed for use at dietary concentrations in excess of 0.1% of the diet, dose-response estimation using animal models would not be appropriate for reasons stated in Chapter III. The traditional approach for generating an ADI, although valid for substances that enter the food supply at low concentrations, must be modified when dealing with macroingredients. In this instance, when animals and humans are administered doses of the test substance sufficiently large to allow determination of a NOAEL in a conventional manner, meaningful results are not obtained. A consequence is that the standard procedure for determining an ADI (NOAEL+100) becomes invalid. Thus, an alternative approach must be employed for assessing the risk associated with consumption of macroingredients that must involve a smaller range of doses than used in conventional studies and a maximum dose that is often not far in excess of the eventual ADI. Furthermore, of necessity, determination of the dose-response relationship must rely much more heavily of tests in humans and less on tests in animals than is true of the conventional approach.
Table 4-5. Linkage of experimental design to safety decisions for new foods and food substances.

<table>
<thead>
<tr>
<th>QUESTION*</th>
<th>CONTROL/DESIGN</th>
<th>SCIENTIFIC INFERENCE/RESULT</th>
<th>SOCIAL INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there any effect of substance X on health attribute Y?</td>
<td>Ingestion of X versus no ingestion of X in subjects receiving otherwise identical care (i.e., diets, environment etc.)</td>
<td>X has (or does not have) an effect on attribute Y.</td>
<td>Yes: X is potentially adverse relative to attribute Y (depending on the social acceptability of the observed effect on attribute Y.) or; No: presumption of safety of X with regard to attribute Y.</td>
</tr>
<tr>
<td>What is the effect of X on attribute Y relative to the effect of foods/ingredients that might be replaced by X (i.e., substance Z)?</td>
<td>Ingestion of X versus ingestion of Z. (in subjects maintained in identical environments with all other dietary factors equivalent: will need to include a pair-fed group in animal studies.)</td>
<td>X has effects that are better, worse, or the same as Z.</td>
<td>Better = presumption of safety of X with regard to attribute Y  Worse = X is potentially unsafe with regard to attribute Y  Same = X might be safe if consumption doesn't increase. Decision will rely on exposure estimates.</td>
</tr>
<tr>
<td>What is the effect of X on attribute Y relative to other foods (W) in the food supply that are known to affect attribute Y?</td>
<td>Ingestion of X versus another food (W) that causes Y, and controls receiving diets devoid of X and W. (in subjects maintained in identical environments with all other dietary factors equivalent: will need to include a pair-fed group in animal studies.)</td>
<td>X has the same, better, or worse effect than W on attribute Y</td>
<td>Better = presumption of safety of X relative to W with regard to attribute Y  Worse = X is potentially unsafe relative to W with regard to attribute Y (assuming the degree of difference meets the criteria of harm).  Same = X might be safe with respect to attribute Y if consumption doesn't increase beyond that of W or is not additive with effects from W. Decision will rely on exposure estimates and severity of the adverse effect.</td>
</tr>
<tr>
<td>What is the effect of X plus W on attribute Y?</td>
<td>Ingestion of X + W versus X alone, W alone, and diet alone (in subjects maintained in identical environments with all other dietary factors equivalent: will need to include a pair-fed group in animal studies.).</td>
<td>Effects of X + W equal the sum of the independent effects of X and W.  Effects of X + W are less than the sum of the independent effects of X and W  Effects of X + W are more than the sum of the independent effects of X + W.</td>
<td>Less = implies a benefit, i.e., X+W are safe for use.  Greater = X+W are unsafe if effect on attribute Y exceeds threshold of harm.  Same = X+Y might be safe with respect to attribute Y if consumption of X+W does not exceed that which has been tested.</td>
</tr>
</tbody>
</table>

* X refers to substances, Y refers to health attributes
However, information garnered from the hazard identification process could be used to identify potential adverse effects that might be the focus of dose-response studies in humans. Irrespective of the subjects to be used in these studies several core concepts need to be addressed, particularly as they relate to substances to be used at dietary concentrations >0.1%. Specifically examples include those concepts related to the generation of the NOAEL and the use of uncertainty factors for the subsequent derivation of an ACI.

As pointed out by Renwick and Walker (1993), the precision of the NOAEL is dependent on three factors:

1) the sensitivity of the endpoints used to defined the risk,
2) the increment between the doses in the dose response study, and
3) the number of subjects used to define the NOAEL.

In the safety evaluation of new foods and food substances, for any given adverse event (variable), the NOAEL is defined as the highest dose at which there is no observed adverse effect associated with the ingestion of the substance in question. Traditionally, “no effect” has been defined as no statistically significant increase in the frequency of the adverse event (or level of the continuous variable) relative to an appropriate control group. The Expert Panel expressed the following concerns about this approach.

Use of the NOAEL is dependent on finding the highest dose level at which the effect is zero. That is, the NOAEL is the highest dose for which one can accept the null hypothesis of no difference between the exposed and unexposed groups. However, a well accepted tenet of experimental design is that one cannot “prove” the null hypothesis with conventional hypothesis testing, one can only fail to reject the null hypothesis (i.e., not obtain a statistically significant result).

A failure to reject the null hypothesis can occur for one of two reasons: (1) the null hypothesis is true; or (2) the null hypothesis is false but the experiment was unable to generate a statistically significant result (i.e., a type-two error occurred). It is impossible to distinguish unequivocally between the two possibilities. Such a distinction can only be made probabilistically. That is, statements about statistical power can be made.

The power of a statistical test is generally denoted as 1-β and represents the probability that a given experimental design will reject the null hypothesis, (i.e., obtain a statistically significant result) given a certain magnitude of the true effect. Therefore, the probability that the same experimental design will result in a type II error (i.e., fail to reject the false null hypothesis) is β. If the experiment is designed such that β is very low then, upon obtaining a nonsignificant result, one can state with a high degree of confidence that the result is unlikely to be a type II error. The problem is that this statement applies only to a particular hypothesized magnitude of effect. For any study of any size one can name a non-zero effect for which power is very low. Thus, one can never justifiably conclude that the study had sufficient power to detect any effect. Consequently, one cannot state that type II errors are unlikely if one is concerned about any non-zero effect. As a result, the NOAEL as traditionally defined represents two indistinguishable possibilities; it is either the highest dose at which there is no effect or the highest dose where there was a type II error. Not only is this conceptually untenable, but it suggests the simplest and most obvious way to obtain a high NOAEL for one’s product is simply to run small or poorly controlled studies of low power.

In defense of the NOAEL one might state that only results from studies of adequate statistical power would be acceptable. With regard to how small an effect could be detected, one might suggest that the effect should be the smallest effect that medicine, tradition, common sense, etc., tells us is of any clinical importance. Using this perspective opens the way for a more logically tenable approach that the Expert Panel considered to be more easily quantifiable, objective, and consistent with the principles outlined in this report.

At each dose level there will be some effect. For the first dose, the effect could be δ. The agreed-upon smallest adverse effect of interest or importance (see definition of adverse effect, Chapter III) would be designated δi, and would be greater than 0. The choice of δi will be a social/policy decision, albeit one that should be made based on the best available scientific information. One can then define an analogous dose which can be called the trivial dose.
"true" t-dose would be defined as the highest dose for which \( \delta_0 < \delta_i \). In practice, an estimate of the t-dose might be the highest dose for which the upper limit of the 100 (1-\(\alpha\))% confidence interval around the estimate is \( \delta_0 < \delta_i \). An example of this approach is depicted in Figure 4-2.

There are several advantages to this approach:

- It is logically consistent with statistical theory in that it does not attempt to prove the null hypothesis (or any other value). Rather, it is designed to demonstrate that a value as large as some prespecified value (\( \delta_0 \)) is very unlikely at a given dose.

- Unlike the use of the NOAEL, this approach rewards rather than penalizes petitioners for conducting larger (therefore more powerful), better controlled studies.

- Finally, it makes explicit the subjective/social nature of the decision about what level of risk is "tolerable" through the necessary specification of \( \delta_0 \). Presumably this decision will be based on sound science and will be made in consort between petitioners, FDA and the consumer community.

d. Risk characterization: premarket

As defined by the NAS, risk characterization is the description of the nature and often the magnitude of human risk, including attendant uncertainty, and "...combines the assessment of exposure and response under various exposure conditions to estimate the probability of specific harm to an exposed individual or population" (NRC, 1993).

The Joint Expert Committee on Food Additives (JECFA) of the WHO and FAO described its current practices for safety evaluation of food additives as a risk assessment in which the hazard identification phase culminates in the derivation of the ADI (Joint FAO/WHO Expert Consultation, 1995). In its application of risk assessment to food standard issues and subsequent generation of an ADI, "JECFA does not make a quantitative estimate of risk at an intake corresponding to the ADI, but concludes that the risk is so small as to be negligible from a public health point of view." This approach is analogous to the current approach employed by the FDA. As delineated in the preceding sections of this report, new foods or food substances for which the Alternative Approach might be applied would require a different approach to risk characterization for the following reasons:

- Many of the new foods and food substances will have a broad distribution in human diets and will be consumed at relatively high levels in the diet.

- The risk characterization will have to account for special consumption patterns in population subgroups, e.g., the elderly or adolescents, and new consumption patterns that might occur as a consequence of the new substance, e.g., changes in consumption of diet beverages consequent to the advent of aspartame.

- The potential impact of secondary constituents of new foods or food substances derived from novel substances or process and that do not meet the standard of substantial equivalence, assumes greater importance than in traditional food additives.

- Identification of susceptible subgroups, e.g., individuals who might be allergic to new foods or food substances, becomes of potentially greater importance with new foods and food substances, particularly those of complex composition and/or those derived from such novel source materials as genetically modified products, than it is with traditional food additives of known chemical nature from conventional source materials and/or with simple structure proposed for use at low (<0.1% of diet) concentrations.
Figure 4-2.

Hypothetical Dose Response Data

\[ \text{delta} = (E-1) \]

\[ \text{delta}_t = 0.002 \]

Dose vs. t-dose graph with error bars.
• The possibility of shifts in nutrient intake and utilization is greater with new food substances such as macronutrient substitutes proposed for use at high concentrations in the diet than it is with traditional food additives.

• Many new food substances will engender concern for potential additive effects between the new substances and one previously approved with similar technical properties.

c. Risk characterization: postmarket

Implicit in the definition of risk assessment and in particular, risk characterization, offered to the Expert Panel by Rodricks (personal communication, 10/25/96) is the need for postmarket surveillance (PMS). PMS is especially important with new foods and food substances to be consumed at high concentrations in the diet as well as those derived from new source materials or new processes that do not meet the standard of substantial equivalence, in part because of the difficulties and limitations of testing such material in animals at concentrations far above that intended in actual use prior to marketing for human consumption.

The FDA has recognized the importance and utility of PMS in recent decisions but has concerns about its utility and application to new ingredients. The Scope of Work (see Chapter I) included several core questions about PMS that reflect the FDA’s concerns.

• Can postmarketing surveillance (both monitoring of use and monitoring of adverse reactions reports by consumers and physicians) be used to ensure safety?

• Can PMS be used without compromising safety to verify exposure estimates or to eliminate the need for specific data prior to marketing, thus reducing the need to use worst case assumptions in a safety evaluation? If so, how could this be accomplished?

Historically, PMS has served two primary functions: to collect and investigate reports of adverse reactions (including identification of idiosyncratic reactions and sensitive subgroups), and to confirm exposure estimates supplied in petitions. Because the Panel has defined safety as a public policy decision reflecting defined societal needs, it is logical to assume that PMS is necessary to ensure the public's continued confidence that the substance in question is safe. Moreover, PMS is an integral part of subsequent rulings with regard to an expansion of the use of a given substance.

Additional uses of PMS include assessment of the impact of macronutrient substitutes (e.g., particularly those with the potential for being consumed as a large part of daily dietary intake, such as fat replacers) on the nutritional intake of the population. As suggested by Cheney (1996), the nutritional impact of macronutrient substitutes can only be determined after the substitute has been approved for use in foods and there is widespread use by the population over time. It is because of the concern about the nutritional impact of such new substances that the Health Protection Branch, Canada's counterpart to the FDA, has proposed mandatory PMS as a condition of approval of macronutrient substitutes and/or extending permitted uses.

If the approach outlined by the Expert Panel in the preceding steps of the safety evaluation process, i.e., exposure estimation, hazard identification, and dose-response assessment, are correctly applied, PMS will serve to confirm the predictions of problems identified in the risk assessment. In addition, potential high-risk groups and idiosyncratic effects could be identified.

Cheney (1996) described surveillance as "the ongoing systematic collection, analysis, and interpretation of selected health-related data closely integrated with the timely dissemination of these data to those who need to know." The

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6 "The systematic organization of available data to evaluate the likelihood (risk) that human populations will experience any of the hazards associated with environmental agents under their actual or projected conditions of exposure." (Rodricks, 1996)
Expert Panel concluded that PMS for new substances could and should be designed to be more than a passive reporting system and petitioners should be required to implement well-designed epidemiological studies intended to achieve the following three goals:

- Establishment of accurate estimates of exposure. PMS should be done in such a way as to generate accurate estimates of the upper levels of exposure, e.g., 90th and 95th percentiles, across pertinent population groups (see Table 9, p.63 of 1988 LSRO report. Anderson, S. A., ed. "Estimation of Exposure to Substances in the Food Supply.")

- Assessment of whether effects generated by the substance in animal and human studies occur in humans under conditions of actual use.

- Detection of possible idiosyncratic reactions in the general population and the identification of sensitive subgroups that might not have been previously identified.

The Expert Panel cautioned that none of these objectives precludes adequate and appropriate premarket testing.

C. CONCLUSIONS

The Expert Panel described the safety evaluation of new foods and food substances as a dialectical process involving the generation of an estimate of risk based on scientific principles and the safety decision made in the context of society's perceived needs. In keeping with the Scope of Work, the focus of this chapter was on the scientific component of safety evaluation.

The traditional approach to safety evaluation of food ingredients has been useful for noncomplex single-chemical ingredients found in low concentrations (generally <0.1%) in the diet. Guided by a set of principles intended to address issues raised by both traditional food additives and new foods and food substances distinguished by their complexity, high (>0.1%) exposure estimates, and/or the novelty of their source materials or production process, the Expert Panel offered a procedure to determine appropriate testing strategies. Whether the choice is traditional animal toxicology tests or the combination of animal testing along with increased emphasis on clinical trials in humans, the Expert Panel viewed the scientific component of safety evaluation of new foods and food substances to be a risk assessment, and as such used the components outlined by the NRC (1982, 1994) in presenting its model.

The Expert Panel recognized that because of the complexity of the subject matter and limitations in time and resources, its presentation was limited primarily to a delineation of the concepts deemed essential to the implementation of its recommendations. The Panel also acknowledged the efforts of a number of organizations and agencies both domestically and internationally who have presented informative and useful descriptions of many of the technical issues pertaining to the safety evaluation of new foods and food substances. As discussed in Chapter II, these authoritative reports outlined many of the technical issues associated with risk assessment of these new materials. However, the Expert Panel was obliged to identify several key technical issues that require further examination:

- Estimation and effective incorporation of uncertainty factors into the risk assessment and risk management process: The Expert Panel has noted throughout this report that a consequence of the advent of the new types of foods and food substances covered in its recommendation is the inability to apply traditional safety factors, e.g., 100:1, in the conduct of animal toxicology tests. The Expert Panel strongly endorsed an expanded discussion of how to identify and quantify those elements that contribute to the inherent variability found throughout the various stages of the risk assessment, i.e., exposure estimation, hazard identification, and quantification of the risk estimate. Many of these issues were addressed broadly in the JECFA report "Application of Risk Analysis to Food Standards Issues," (Joint FAO/WHO, 1995). The Panel urged an expansion of this discussion.
An additional, albeit abbreviated, list of papers addressing the question of uncertainty in the context of food safety evaluation includes Calabrese, 1985; Renwick, 1993a, b, 1995; Rulis, 1991.

A detailed description of the process for the generation of a quantitative measure of risk: the ADI has been the traditional endpoint in the safety evaluation of new foods and food substances. The Expert Panel adopted the term acceptable chronic intake (ACI) as being more reflective of the goal of the risk assessment. However, a more detailed discussion will be needed of how that estimate is derived. In particular, specific attention must be paid to the process for assessing potential chronic effects.

As noted throughout this report the potentially high levels of exposure of some new foods and food substances obviate the traditional approach to the use of animal studies and necessitate the increased use of clinical trials in humans. However, a limitation of human trials in the premarket phase of the risk assessment is the difficulty in conducting long-term trials. Consequently, chronic animal studies will continue to play an important role in this part of the assessment process. The choice of appropriate markers/ endpoints, and the nature and dose of the substances to be evaluated must be based on the best available science and an effective dialogue between the petitioner and the scientific staff of the FDA or appropriate regulatory agency.

In addition, an expanded coverage will be needed for how a quantitative risk estimate for the general population and for specific "at risk" groups will be generated and subsequently implemented in the risk management phase of the evaluative process.


Case-study applications of the alternative models: the Expert Panel strongly encourages the application of the proposed model to hypothetical cases of new foods and food substances in order to work out the details, e.g., estimation of appropriate doses for control substances to be used in some of the hypothesis testing protocols, outlined in Table 4-5, of the process prior to its implementation.

Recommendations about which tests to use to support a petition for a new food or food substance have historically been, and will continue to be, made by the highly qualified scientists of the FDA with an appreciation for the evolving state of the science and resource availability. Irrespective of the choice and methods used, the end result of this process must be the generation of a science-based reliable and valid estimate of risk that can be used to make a safety decision that will meet the standard of a "reasonable certainty of no harm."
V. RESPONSES TO QUESTIONS POSED IN THE SCOPE OF WORK

In framing the discussions for the report, the FDA suggested that the following questions be considered. These questions were not intended as a statement of specific tasks. They were intended to be illustrative and to be used to stimulate thought regarding the determination of the safe use of new foods and food substances. The following is a presentation of the questions and responses based on materials presented in the body of the report. For ease of presentation, each question is divided into its constituent parts. Along with the response, the reader is referred to relevant sections in the body of the report for additional material.

1A. In what cases are animal feeding studies not necessary to ensure safety?

In part, the question faced by the Expert Panel was how to address situations because of the nature of the materials tested, i.e., composition and estimated exposure, obviates the use of animal models to generate relevant data upon which to base a safety decision. Because the traditional approach as reflected in the recommendations for testing outlined in the Redbook (FDA, 1982) limited the criteria for determining testing to structure category and exposure estimates, the Expert Panel concluded an alternative approach was required to address more effectively questions raised by the advent of new foods and food substances derived from novel source materials, from new production methods and/or with high estimated exposures.

The Alternative Approach presented by the Expert Panel in Chapter IV, which includes elements of the traditional approach presented in a new classification scheme to replace the previous concern level approach, is a recognition of the need for a synergism between animal testing in the traditional toxicological sense and clinical trials in humans. The advent of new foods and food substances of increasing complexity, derived from novel source materials and production methods, and with potentially high exposure scenarios requires a process that has a greater emphasis on human clinical trials to assess risk1. According to Redbook II (FDA, 1993), clinical trials in humans should be preceded by toxicological testing in animals designed to establish "confidence in the safety of the product for human consumption." Consequently, even though the emphasis on animal testing is greatly diminished in the Alternative Approach, such testing will continue to be an integral part of the evaluation process.

The Expert Panel recognized that for many of the substances in question, it might be possible to identify and quantify an adverse effect in an animal test during the hazard identification phase of the assessment process. The Expert Panel understood that a core issue in the decision to use the traditional and/or an alternative approach is the inverse relationship between the novelty of the substance in terms of source materials and production process, complexity, and/or exposure and confidence in the traditional approach. For example, as exposure estimates increase, confidence in traditional toxicological approaches decreases. To a large degree, this lack of confidence relative to the safety evaluation of many new foods or food substances, e.g., fat substitutes, is due to the confounding effects on nutrition, and/or the inability to identify and fully characterize adverse effects in humans from data obtained with animal models.

More specifically, the Expert Panel identified several key limitations of the use of standard animal-based toxicological testing, for those substances that are either complex mixtures, derived from new source materials or are products of new production methods, and/or whose exposure is estimated to exceed 0.1% of the diet. Among these limitations are:

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1 The Expert Panel recognized that because of logistical reasons, e.g., subject availability/compliance, resource limitations, etc., the focus of clinical studies in humans would be on acute effects, thereby necessitating the continued use of long-term animal studies. The nature, i.e., parent compound versus sub-components/metabolites, and dose of the materials to be tested in such studies would be based on the characterization phase and an interaction between the petitioner and FDA scientific staff.
Either because of their subjective nature or differences in physiology and/or metabolism, suitable animal models may not exist that could be used in studies intended to assess the comparative effects/hazards associated with consumption of new ingredients by humans, e.g., gastrointestinal intolerance.

Potential effects may occur that lack relevant or known biological markers, particularly in animal models, e.g., headache or allergy.

In cases where the use of the new substance is projected at levels approaching the estimated daily intake (EDI), effects in animals could be associated with changes in nutrition rather than direct effects from the substance being evaluated. In this regard, based on its understanding of the universe of substances to be covered in this report and the principles laid out in Chapter III, the Expert Panel concluded that an approximate value of 0.1% of the diet would serve as the reference point beyond which alternative approaches to safety testing outlined in Chapter IV would be required.

The Expert Panel’s concerns about the reliance on the traditional use of animal studies may be attributed to the fact that many of these proposed substances exceed a concentration of about 0.1% of the diet. The Expert Panel concluded that the safety evaluation leading to the determination of the acceptable chronic intake of any new food ingredient proposed for use at a dietary concentration in excess of 0.1% cannot be accomplished reliably by traditional methods.

The 0.1% concentration level was deemed “critical” because traditional animal testing protocols generally involve testing substances at a range of concentrations, the high end of which is much greater (100- to 1000-fold) than that intended for eventual use in human diets. This range is tested to define a dose-response relationship, to establish a no observable adverse effect level (NOAEL), to estimate a safety factor, and to determine an ADI. If the proposed substance is intended for use at 0.1% in the diet, then a 100-fold elevation in animal diets would result in a diet concentration of 10%, which would be sufficiently large to cause confounding dietary imbalances, the possibility of “pseudo-toxicity” resulting from chronic changes in physiological homeostasis, occasional problems of diet rejection by test animals, and in general, a greatly decreased ability to determine accurately the intrinsic toxicity of the substance. Thus, as the proposed concentration of a new substance in the human diet increases above 0.1%, traditional animal testing protocols become increasingly inapplicable.

The Expert Panel viewed this question has having several additional nuances:

Presumably, this question, in part, is focused on the issue of threshold of regulation (TOR). As described by Rulis (1992), TOR applies primarily to indirect food additives and is largely quantitative, i.e., based on "extremely low exposure to food chemicals migrating to food from food-contact materials..." The regulation of such substances must be done on a case-by-case basis for two reasons: (1) there is no floor of exposure under which any additive is exempt from the premarket approval process, and (2) the Delaney Clause mandates that no carcinogen no matter what the exposure can be added to the food supply. It is unlikely that any of the types of novel substances considered by this Panel would qualify for a TOR determination based on estimated exposure.

Flamm et al. (1994) pointed out that the decision tree outlined in the Redbook for establishing concern levels (CL) is in effect a TOR. For example, a substance of a particular structure with a projected exposure under specific conditions of use may not require certain types of testing. The Expert Panel noted that the exposure criterion (>0.1% of the diet) and the comprehensive chemical characterization of the substance in question may serve as a TOR process by predicting the need for testing. Conceivably, if a substance is derived from a food using an accepted production process, and careful characterization and review of relevant literature...
raise no health concerns, i.e., meets the standard of substantial equivalence\(^2\), there would be no further need for premarket testing. Postmarket surveillance would confirm (or not) the ingredient's safety in all segments of the population.

In the case of genetically modified foods, the TOR would presumably be based on the standard of substantial equivalence. In other words, if the manufacturer can establish with reasonable certainty that the "new" food is substantially equivalent to the "old" food, no additional testing would be required. This is essentially the position outlined by the FDA (1992) and numerous authoritative groups and organizations (see Chapter II for detailed discussion of these positions).

The Expert Panel agreed with the position of the Joint FAO/WHO Consultation (1996) that the determination of substantial equivalence relative to new foods requires a consideration of the molecular characteristics of the new food source, phenotypic characterization of the new food source in comparison to an appropriate comparison food already in the food supply, and a compositional analysis of the new food in comparison to preexisting comparison food. In cases of new substances that might have an equivalent composition, if the substance is derived from a different genetic source than the comparison acceptable food, then the new substance would not meet the standard and would require testing to ensure that its meets the standard of safety, i.e., reasonable certainty of no harm. (See Chapter III, section A-1 for expanded discussion of substantial equivalence).

* Taken at face value, one would assume that substances that occur naturally in food, and whose potential exposure based on proposed conditions of use is consistent with historical use patterns would not necessarily require extensive animal testing. However, as witnessed by the situation with glutamates, it may be that questions need to be answered about potential differences between the substance in its natural milieu as opposed to the extracted substance used in isolation to impart a particular effect. In the latter case one would presume some degree of absence of risk, but would certainly want reasonable certainty that the use as requested would be harmless.

To summarize, the Expert Panel concluded that the question is not whether animal testing can be used, rather where and how. Clearly, animal testing can provide some useful information about potential adverse effects irrespective of the nature of the new substance or its concentration in the diet. However, particularly for those substances that will be used at concentrations >0.1%, it would not be possible to use animal testing to establish a dose-response relationship, NOAEL, and subsequent ADI. For those new substances that might be used at concentrations below 0.1%, animal testing may reveal effects, e.g., nutritional imbalances or disruptions in nutrient utilization, neuroendocrine or behavioral effects, that would require clinical trials in humans to establish the extent of adverseness.

Although recognizing that decisions must be made on a case-by-case basis, the Expert Panel identified the following cases where animal testing might not be required:

- substances with an accepted specification;
- substances meeting the standard of substantial equivalence, and
- substances where exposure is not materially increased, i.e., where the substance is a substitute rather than an addition to the food supply.

\(^2\) The Expert Panel offered the following definition of substantial equivalence: Any substance that is essentially identical in terms of phenotypic characteristics, composition, and genetic origin to a substance already in the food supply, provided the existing substance, at the concentration being considered, is regarded as acceptable by scientists and medical personnel with expertise in evaluating human health and food safety.
1B. As examples, do such studies need to be conducted for ingredients that also occur naturally in foods at similar or higher concentrations?

In Chapter III, the Expert Panel explored several potential hypotheses that might be tested in conjunction with a risk assessment. The answer to the question is yes and the justification for this answer is found in the following case study.

In cases where experiments involve comparison of the proposed substance’s effects with those of a substance that is similar in nature, and which occurs naturally in the food supply, e.g., comparison between chemically modified hydrocolloid and a natural fiber, projected exposure becomes a critical factor in interpreting the results. Experiments of this kind inevitably lead to interpretations based on the assumption that the naturally occurring control substance has effects that are “common and acceptable” in the general population, as well as relevant population subgroups. As demonstrated in the following case study in which ringing in the ear or tinnitus is the suspected adverse effect, this assumption needs to be examined with care. One reason for selecting tinnitus as the hypothetical adverse effect is that a suitable animal model is not available, thereby necessitating trials in humans.

Case study:

Macroingredient, MI is proposed as a new food additive. MI is known to cause increased incidence of tinnitus when used at high concentrations, and its functional properties are similar to those of substance C, which occurs naturally in many foods at substantial concentrations. C is therefore selected as a “control” substance for assessing the safety of MI. Assume the following is known about the effects of C on tinnitus:

<table>
<thead>
<tr>
<th>Exposure (eaters only)</th>
<th>Incidence (% of population)</th>
<th>Tinnitus Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentile</td>
<td>grams/day</td>
<td></td>
</tr>
<tr>
<td>50th</td>
<td>2</td>
<td>$10^{-5}$</td>
</tr>
<tr>
<td>90th</td>
<td>4</td>
<td>$10^{-4}$</td>
</tr>
<tr>
<td>99th</td>
<td>8</td>
<td>$10^{-3}$</td>
</tr>
</tbody>
</table>

Assume that the effects of MI on tinnitus are the same as those of C at any given level of exposure. At the three levels of exposure, what might be an acceptable judgement regarding “reasonable certainty of no harm?”

- If MI is proposed at a 50th percentile maximum exposure of 2 gram/day a positive judgement would be justified.
- If MI is proposed at a 90th percentile maximum exposure of 4 grams/day a positive judgement would be questionable;
- If MI is proposed at a 99th percentile maximum exposure of 8 grams/day a positive judgement would not be justifiable.

The principle demonstrated by this case study is that judgements about whether adverse effects of naturally occurring components of human diets are or are not “common and acceptable” must account for the level of exposure in humans. This principle is applicable in cases where substantial equivalence is proposed as a criterion for safety testing and/or acceptability. For example, in the 99th percentile example, the establishment of substantial equivalence to a
conventional food or food substance would clearly not be an acceptable standard for affirming a "reasonable certainty of no harm."

To summarize, the need for animal studies will depend on the EDI if the material meets the standards summarized in question 1A above. If the substance is to be used at high concentrations and meets the criteria as laid out in the Decision Tree, then studies should be required in a manner described in Chapter IV.

1C. Is it reasonable and necessary to test food-like substances for toxicity and nutritional influences, recognizing the potential for confounding results? If so, how?

Yes. As described in Chapter IV, whether or not a substance should be tested is based on its proposed conditions of use, composition, and/or the source materials or process for production. As emphasized in Chapter III and in the justification of the decision tree presented in Chapter IV, the question of whether the substance is "food-like" should not be the test for a decision about testing. The obstacles raised by the complexity of the substance will need to be addressed scientifically as described in Chapters III and IV.

Whether a substance should be tested and if so, whether to apply the traditional or alternative approach are addressed by the Panel's decision tree and proposed classification scheme presented in Chapter IV.

Part of the focus of this question appears to be on the issue of experimental design and selection of controls. Elements of both of these issues are addressed in Chapter III and Chapter IV. Presumably, at least part of the issue raised by this question is the case where a new ingredient will be used at a high enough level in the diet to make the generation of an ADI from animal studies unrealistic. In addition to the chemical/physiologic/metabolic characterization incumbent in Step 1 of the of the Alternative Approach recommended by the Panel, it would be important to address the issue of experimental design in those studies intended to test such food-like substances. Meta-analytical approaches would also be useful in evaluating relevant clinical studies.

2. To what extent can chemical and structural similarity to food ingredients known to be safe obviate the need for animal or human testing?

It is conceivable in an individual case that the prerequisite chemical/physiological/metabolic evaluation would provide sufficient evidence to render subsequent testing unnecessary. However, it would be unwise to base all decisions relative to threshold of testing on structural similarities, particularly for those substances with exposure estimates exceeding 0.1% of the diet.

3. What criteria should be used to determine when a treatment-related effect (including effects from nutritional imbalance or interference) is an adverse effect?

The Panel offered the following definition of adverse effect in Chapter III.

An adverse effect in humans occurs when ingestion of a substance causes an effect, (i.e., a biochemical change, functional impairment, or pathological lesion), that either directly or indirectly adversely affects performance or reduces one’s ability to respond to an additional environmental challenge.

To put this definition in perspective and within the context of safety evaluation of new substances to be included in the food supply, an additional question must be answered. "When is an adverse effect sufficiently serious so that a new food or food substance fails to meet the standard of "reasonable certainty of no harm?" The Expert Panel provided the following criterion to address this question:
When an adverse effect caused by the substance at a specified exposure, exceeds the frequency and severity that have been established by scientists and medical experts with expertise in evaluating human health and food safety, as common and acceptable in the general population and in relevant sub-groups thereof, then the new food or food substance exceeds the threshold exposure for harm, i.e., it fails to meet the standard of "reasonable certainty of no harm."

Implicit in the Expert Panel's definition of adverse effect is the acceptability of trivial adverse effects. In its definition of adverse effects, i.e., the effects that the new compound produces under proposed conditions of use, the Panel acknowledged that effects may occur but that historically, the community has recognized the extent and nature of the effect as being trivial and generally regarded from a clinical perspective as being acceptable. For example, if a nutritional imbalance or interference associated with the consumption of a new substance does not meet this standard of triviality, then it would be considered an adverse effect. This presupposes that the effect was uncovered using a validated standardized assessment parameter accepted by the scientific community for the definition of the particular nutritional imbalance in either an animal or a clinical study.

Perhaps what is really being asked here is when is such an effect significant relative to the "background" that currently exists in the food supply. As stated in Chapter III the Expert Panel recognized that the term "background noise" is used in the context of risk assessment. However, the Panel viewed the term as nebulous and potentially subject to misuse. For example, if a substance causes headache in 10% of the sample studied, that effect could be dismissed as equivalent to the "background noise" (assuming an incidence of 10% in the general population). However, if the 10% experiencing headache in the trial normally did not experience headache, then to dismiss the outcome as unimportant because it does not exceed the "background noise" in the general population would be inappropriate. In general, the Expert Panel viewed the "background noise" as more a reflection of the variability in the general population than a standard for comparison.

Thus, to compare the effects of a new food substance to those that might occur in the general population consuming a variety of foods is useful to gain an appreciation for the risk, to put the risk into some context, and to give perspective; however, under no circumstances should such comparison be in and of itself justification for an added risk associated with a new ingredient or be sufficient grounds for a safety decision. For example, the general population may exhibit a distribution with respect to a given health attribute, such as bone density, frequency of headache, or blood pressure, that should not be regarded as an acceptable standard. This emphasizes the need to select experimental control conditions that accurately represent acceptable and realistic standards of health.

4. Are there criteria that can be used to determine whether an adverse effect observed in a study is relevant to human safety, as opposed to an effect that is dependent on study design and has no relevance to safety under actual use conditions?

The Expert Panel offered the following suggestions regarding the design of experiments and selection of appropriate controls (see Chapter III).

Implicit in the "degree or persistence of adverseness that has been established by medical experts as normal in the general population" is the question of what constitutes a reasonable standard for comparison or "control" to establish whether an effect occurs and is harmful. In an experimental setting, the choice of a control sample is inextricably linked to the question one is asking regarding the substance, i.e., what types of adverse effects are of interest?, and may differ depending on the attribute under study. The choice of what level/type of attribute is of interest and considered "adverse," though based on sound scientific principles, is ultimately a social/policy decision. Several examples of study objectives and associated control sample types exist; among them are:

- "Zero-tolerance" - This represents an absolute standard of no adverse effect. The most obvious example of the utility of this study objective is the occurrence of cancer. An acceptable test result requires that the
incidence of cancer in suitable types and numbers of animals fed the test substance at various concentrations and for an appropriate time is not significantly greater than that in the control population.

- Use of a control substance that is not functionally similar to the test substance. This scenario would only be considered when a functionally similar substance does not exist in the food supply. In this instance, one might consider the test substance harmful only if it has adverse effects that are meaningfully more severe than a currently used substance that is legally safe, is not functionally similar, but has the greatest similarity to the test substance of any substance existing in the food supply. For example, dietary fiber of some type might be a reasonable control substance for a nondigestible macronutrient substitute.

- Use of a control substance that is functionally similar to the test substance. In this instance, one might consider the substance harmful only if it has effects that are worse by some degree than a currently available substance that is legally safe and is functionally similar to the test substance. For example, the dietary component being replaced (e.g., starch) would be a reasonable control substance for the test substance (e.g., a chemically modified starch).

- Use of multiple controls. For thorough assessment of substance risk, it will often be necessary to conduct several animal experiments using different types of control samples—the specific types being dictated by the experimental objectives.

In addition, the Expert Panel offered suggestions on the types of hypotheses that might be tested relative to the evaluation of new foods and food substances. As outlined in Chapter IV the hypotheses and approaches to testing are summarized in the following table in which experimental design is linked to safety decisions.

The provision of tentative answers to these questions and the design of experiments to provide those answers flow directly from well-established scientific practices and principles. Nevertheless, the selection of what question is of interest or what comparator can set the standard of “not adverse” must be acknowledged as a social/policy decision.

With regard to possible standards, the Expert Panel judged the standard of absolute safety, i.e., no effects, to be impractical for most effects. In fact, the codified use of uncertainty factors, by implication excludes the consideration of absolute safety for food ingredients.

The criteria to be applied to studies in humans designed to identify adverse effects would include:

* universally accepted criteria for experimental design, in particular careful selection of control substances and control groups;

* testing would have to include administration of substances in situations both short- and long-term that would be analogous to conditions of use; and

* effective hazard identification and exposure assessment procedures will enable the generation of realistic dose-response curves. In particular, the exposure assessment phase will allow for the identification of realistic doses to be used in studies.
<table>
<thead>
<tr>
<th>QUESTION*</th>
<th>CONTROL/DESIGN</th>
<th>SCIENTIFIC INFEERENCE/RESULT</th>
<th>SOCIAL INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there any effect of substance X on health attribute Y?</td>
<td>Ingestion of X versus no ingestion of X in subjects receiving otherwise identical care (i.e., diets, environment etc.)</td>
<td>X has (or does not have) an effect on attribute Y.</td>
<td>Yes: X is potentially adverse relative to attribute Y (depending on the social acceptability of the observed effect on attribute Y); No: presumption of safety of X with regard to attribute Y.</td>
</tr>
<tr>
<td>What is the effect of X on attribute Y relative to the effect of foods/ingredients that might be replaced by X (i.e., substance Z)?</td>
<td>Ingestion of X versus ingestion of Z. (in subjects maintained in identical environments with all other dietary factors equivalent: will need to include a pair-fed group in animal studies.)</td>
<td>X has effects that are better, worse, or the same as Z.</td>
<td>Better = presumption of safety of X with regard to attribute Y; Worse = X is potentially unsafe with regard to attribute Y; Same = X might be safe if consumption doesn't increase. Decision will rely on exposure estimates.</td>
</tr>
<tr>
<td>What is the effect of X on attribute Y relative to other foods (W) in the food supply that are known to affect attribute Y?</td>
<td>Ingestion of X versus another food (W) that causes Y, and controls receiving diets devoid of X and W. (in subjects maintained in identical environments with all other dietary factors equivalent: will need to include a pair-fed group in animal studies.)</td>
<td>X has the same, better, or worse effect than W on attribute Y</td>
<td>Better = presumption of safety of X relative to W with regard to attribute Y; Worse = X is potentially unsafe relative to W with regard to attribute Y (assuming the degree of difference meets the criteria of harm); Same = X might be safe with respect to attribute Y if consumption doesn't increase beyond that of W or is not additive with effects from W. Decision will rely on exposure estimates and severity of the adverse effect.</td>
</tr>
<tr>
<td>What is the effect of X plus W on attribute Y?</td>
<td>Ingestion of X + W versus X alone, W alone, and diet alone (in subjects maintained in identical environments with all other dietary factors equivalent: will need to include a pair-fed group in animal studies.)</td>
<td>Effects of X + W equal the sum of the independent effects of X and W. Effects of X + W are less than the sum of the independent effects of X and W Effects of X + W are more than the sum of the independent effects of X + W.</td>
<td>Less = implies a benefit, i.e., X+W are safe for use. Greater = X +W are unsafe if effect on attribute Y exceeds threshold of harm. Same = X+Y might be safe with respect to attribute Y if consumption of X+W does not exceed that which has been tested.</td>
</tr>
</tbody>
</table>

* X refers to substances, Y refers to health attributes
5. Under what circumstances should clinical studies in humans supplement, or replace, studies in laboratory animals? Which parameters should be measured and what study duration is necessary?

In a sense human studies are performed in all cases either in the premarket phase, in which clinical trials might be used to replace or supplement animal studies or in the postmarket phase in which postmarket surveillance is used to confirm the findings of the hazard identification phase. In the premarket phase, human studies would replace animal studies in those cases where the exposure estimations indicate a dose that would be unrealistic for use in animals or in those situations where the potential effect is not testable in animals.

In those cases involving substances with exposure estimates >0.1% of diet, where animal studies are conducted, the mechanism of any identified potential adverse effects would have to be identified in order to determine whether those effects are due to the substance or are secondary effects from dietary changes.

If testing is performed in humans, it would have to be preceded by data indicating a degree of certainty of no harm to subjects in such trials. This could be reasonably assured by the careful evaluation of the chemical composition and metabolism data and selected animal testing protocols.

Provided the in vivo animal studies demonstrate no adverse effects, consideration could be given to conducting a series of investigations in humans. The purpose of these investigations would be to confirm the absence of metabolic and physiological disturbances in humans and thereby assess the relevance of experimental findings to humans. Several factors should be considered in the careful design of human trials:

- Because of the well-recognized impact of bolus feeding of nonnutritive substances on intestinal transit time and gastrointestinal function, human studies must involve incorporation of the test material into food.

- The test material should be consumed via the intended food matrices, employing the consumption pattern and daily frequency typically associated with the elected food types, and

- The dose levels should span the range of the projected mean and upper level of intake, i.e., 90th percentile or higher where possible, calculated from proposed use patterns.

The following is a listing of Clinical Parameters Relevant to the Safety Assessment of New Foods and Food Substances

<table>
<thead>
<tr>
<th>Category</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical observations</td>
<td>General health status (including immune response, behavioral/ cognitive function, neurological exam)</td>
</tr>
<tr>
<td></td>
<td>GI tolerance</td>
</tr>
<tr>
<td></td>
<td>Stool consistency</td>
</tr>
<tr>
<td>Clinical hematology and chemistry</td>
<td>Hematology</td>
</tr>
<tr>
<td></td>
<td>Serum chemistry</td>
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<tr>
<td>Urinalysis</td>
<td>Volume</td>
</tr>
<tr>
<td></td>
<td>Electrolytes</td>
</tr>
<tr>
<td></td>
<td>Tissue damage markers</td>
</tr>
<tr>
<td>Nutrient balance</td>
<td>Fecal/urine composition</td>
</tr>
<tr>
<td>Energy utilization</td>
<td>Fecal energy</td>
</tr>
<tr>
<td></td>
<td>Urinary energy</td>
</tr>
</tbody>
</table>
6. **Is there an agreed-upon basis for determining the maximum level of an additive in a test diet, above which a study should be presumed unacceptable?**

Presumably, this question refers to the conduct of animal studies. A critical issue in the conduct of animal studies of substances proposed for use at high dietary concentrations is the difficulty in interpreting the results of such studies, i.e., the difficulty in determining whether the observed effects are caused by intrinsic toxicological properties of the test substances, or by nutritional imbalances secondary to the exaggerated doses customarily used. More specifically, in the decision tree presented in Chapter IV, the criterion for decreased confidence in animal testing is an estimated exposure level of >0.1 the diet. This concentration was chosen as a reference point because substances present at concentrations >0.1% cannot be evaluated in animal trials using the 100:1 uncertainty factor approach. The choice of this criterion is based on the assumption that tests conducted using the substance at a dietary concentration >10% will lead to results that are not meaningful.

However, it should be noted that the achievement of this criterion, i.e., estimated exposure >0.1%, does not necessarily exclude the possibility of performing animal studies as exemplified by the following two cases:

- As stated previously, if an effect is uncovered in animal studies involving doses above the threshold of >0.1% of the diet, then the mechanism of action will have to be determined in order to rule out secondary effects from the dietary manipulations versus primary effects from exposure to the substance. In other words, it is not necessarily the case that the results of animal testing would be unacceptable, rather the issue is how the results are interpreted and utilized. In cases of substances with high exposure estimates, the results may be used appropriately to confirm or identify potential effects, but it would be unlikely that such tests could be used to generate a realistic NOAEL and subsequent acceptable chronic intake (ACI) without some clear understanding of the mechanism(s) of the effect.

- In the case of a complex substance with an exposure estimation beyond the criterion, animal tests could be performed on the components and/or the metabolites of the substance at exaggerated doses to test for adverse effects and to even generate accurate, realistic NOAELs for these sub-components. The results of these tests could then be used in making decisions about the parent compound.

7. **Can postmarketing surveillance (PMS) (both monitoring of use and monitoring of adverse reactions reports by consumers and physicians) be used to ensure safety?** For example, can it be used without compromising safety to verify exposure estimates or to eliminate the need for specific data prior to marketing, thus reducing the need to use worst case assumptions in a safety evaluation? If so, how could this be accomplished?

Historically, PMS has served two primary functions: to collect and investigate reports of adverse reactions, and to confirm exposure estimates supplied in petitions. PMS is an essential part of ensuring substance safety under actual conditions of use. Moreover, PMS would enable the FDA to rule intelligently on subsequent requests to authorize new uses and/or higher concentrations of the substance in question.

Uses of PMS include assessment of the impact of macronutrient substitutes (particularly those with the potential for being consumed as a large part of daily dietary intake, such as fat replacers) on the nutritional intake of the population. As stated by Cheney (1996), "the nutritional impact of macronutrient substitutes can only be determined after the substitute has been approved for use in foods and there is widespread use by the population over time." It is because of the concern about the nutritional impact of such new ingredients that the Health Protection Branch, Canada's counterpart to the FDA, has proposed mandatory PMS as a condition of approval of macronutrient substitutes and/or extending permitted uses, a policy endorsed by the Expert Panel.

If the approach outlined by the Expert Panel in the preceding steps of the safety evaluation process, i.e., hazard identification, dose-response assessment, and exposure assessment, is correctly applied, PMS will serve to confirm the
predictions of problems identified in the safety evaluation. In addition, potential high-risk groups and idiosyncratic effects could be identified.

In summary, the Expert Panel concluded that PMS can and should be designed to be more than a passive reporting system and petitioners should be required to implement well-designed epidemiological studies intended to achieve the following three goals:

1. Establishment of accurate estimates of exposure. PMS would need to be done in such a way as to generate accurate estimates of the upper level of intake, e.g., 90th and 95th percentiles, across various population groups (see Table 9, p. 63 of 1988 LSRO report "Estimation of Exposure to Substances in the Food Supply").

2. Assessment of whether predictions of effects generated from animal studies and limited studies in humans are born out in the population of exposed humans.

3. Detection of possible idiosyncratic reactions in the general population and the identification of sensitive subgroups that might not have been previously identified.

The Expert Panel cautioned that none of these reasons should substitute for adequate and appropriate premarket testing.
VI. REFERENCES CITED


Merrill, R. (1996) Personal communication with Daniel J. Raiten, Ph.D., Senior Staff Scientist/Project Director, Life Sciences Research Office.


VII. STUDY PARTICIPANTS

A. AD HOC EXPERT PANEL

David Allison, Ph.D.
Obesity Research Center
St. Luke's-Roosevelt Hospital
Columbia University
College of Physicians and Surgeons
New York, New York

Owen R. Fennema, Ph.D.
Professor
Department of Food Science
University of Wisconsin
Madison, Wisconsin

Kate L. Clancy, Ph.D.
Henry Wallace Institute
Greenbelt, Maryland

Sanford Miller, Ph.D.
Dean, Graduate School of Biomedical Science
University of Texas Health Science Center
San Antonio, Texas

Ian C. Munro, Ph.D.
Principal
CanTox, Inc.
Mississauga, Ontario
Canada

B. FOOD AND DRUG ADMINISTRATION

Fred R. Shank, Ph.D.
Senior Advisor to the Commissioner
Food and Drug Administration
Rockville, MD

Victor P. Frattali, Ph.D.
Special Assistant to the Deputy Director for Programs
Center for Food Safety and Applied Nutrition
Food and Drug Administration
Washington, DC

Alan M. Rulis, Ph.D.
Director
Office of Premarket Approval
Center for Food Safety and Applied Nutrition
Food and Drug Administration
Washington, DC

James T. Tanner, Ph.D.
Special Assistant to the Director
Office of Special Nutritionals
Center for Food Safety and Applied Nutrition
Washington, D.C.

C. LIFE SCIENCES RESEARCH OFFICE STAFF

Michael Falk, Ph.D.
Director

Carol A. Riley
Administrator

Coleen Kitaguchi
Administrative Secretary

Donald G. Smith
Literature Retrieval Librarian

Daniel J. Raiten, Ph.D.
Senior Staff Scientist

John M. Talbot, M.D.
Senior Medical Consultant
VIII. ORGANIZATIONS SUBMITTING INFORMATION ON ALTERNATIVE AND TRADITIONAL MODELS FOR SAFETY EVALUATION OF FOOD INGREDIENTS

A. OPEN MEETING PARTICIPANTS

The Open Meeting on Alternative and Traditional Models for Safety Evaluation of Food Ingredients was held May 15, 1996. One (1) oral presentation was made.

Robert Smith
The Flavor and Extract Manufacturers’s Association
Washington, DC

B. WRITTEN COMMENTS

The following organizations submitted written materials for consideration by the ad hoc Expert Panel:

Richard M. Clark
Marilyn Schramm
Kellogg Company
Battle Creek, Michigan

Daniel G. Steffen
ILSI North America
Washington, DC

Alice J. Caddow
Enzyme Technical Association
Washington, DC

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1 Copies of the Open Meeting transcript are available from Ace-Federal Reporters, 1120 G Street, NW, Washington, DC 20005.
APPENDIX A

SOLICITED COMMENTS
RESPONSE #1

A. Alan Moghissi, Ph.D.
President
Institute for Regulatory Science
P.O. Box 7166
Alexandria, VA 22307

Thank you for your letter of November 3, 1995 and the extension of deadline provided in your letter of January 17, 1995. In my judgement, FASEB is uniquely qualified to conduct the study and thus providing an important service to FDA and ultimately to the nation. It is imperative that government agencies recognize the role of the scientific community including the ability to study specific subjects that no government agency can conduct. Essentially all regulatory agencies have a mandate to advocate a certain cause and advocacy requires a bias which makes it inherently inconsistent with the ability to perform independent studies.

Food is a necessity for sustenance of life. Although food is abundant in the US and in many industrialized countries, one should not lose sight that lack of food is just as unacceptable as unsafe food. Our food safety system is based on the implicit assumption that whole foods that have not been subjected to human intervention contain no hazardous substance. The rational for this assumption is that during the human evolution materials that were hazardous caused harm to those who consumed it and thus were eliminated from consumption. This assumption overlooks the fact that until about a century ago, the predominant cause of death was infectious diseases. Therefore, only those foods that caused acute and possibly subchronic poisoning were detected and eliminated from usage. There was no mechanism to eliminate whole foods that contained trace quantities of hazardous substances. Advancements in analytical chemistry and toxicology have only recently identified trace quantities of substances that are highly hazardous if consumed at sufficient quantities.

The Paracelsus principle is as applicable to substances constituting food as to any other substance. Accordingly, excessive intake of substances constituting food will undoubtedly cause toxic reactions. It is true that the size of the human stomach places limitations on the intake of toxic levels of many food items, however, this limitations apply to those substances that are required in large quantities such as proteins, carbohydrates, and to a lesser extent fatty substances. Almost all other materials can be taken in sufficient quantities to cause toxic effects. Materials that are added to food for the purpose of enhancement of certain aspects of the food must be considered in the context of the Paracelsus principle. For example, regardless of the legal definition, spices can be classified as additives just as preservatives are additives.

There appears to be some confusion on what constitutes food treatment. Most food is processed either by the producer, processor, or consumer to insure its acceptability. A similar situation exists on food safety. The confusion on the meaning on what constitutes a safe food is even greater than the confusion on treatment. A safe food should not be construed to be risk free. The advocates of risk-free food would be hard pressed to find any food that does not contain a material that poses some level of risk.

The objective of food safety management must be to keep the risk associated with consumption of food significantly below the benefits that are derived from that food. In particular, it is imperative to recognize that one of the most fundamental aspects of risk-benefit (or cost-benefit) assessment is that those who are exposed to risk must be the primary beneficiaries of the benefit. At a minimum they must receive a significant benefit.

Safety assessment of any product or process requires an evaluation of potential adverse effects, their magnitude and methods for their elimination, or at least reduction. These adverse effects must be then compared with advantages of the product. This process must be repeated for alternatives to the proposed product or process. The scientific discipline that covers the processes described above is risk analysis. In its most general, form, risk analysis consists of risk assessment, risk management, and risk communication. Risk assessment is the scientific and technical process of establishing and quantifying a potential adverse effect
associated with an activity. Risk management is based on risk assessment and considers cost, socio-political, legal cultural and other parameters. Risk communication consists of informing the public particularly those who are exposed to risk on risk management decisions and the information that led to that decision. Enclosed is an article describing the risk analysis process and its applications.

In the context of food safety, parameters that are of particular interest are as follows:

1. What are the risks of the process or the substance to a person who has a lifestyle which is within the range of what is currently considered to be "normal"?

2. What are the risks of the process or the substance to a person who is significantly outside of the normal range?

3. What are the benefits from the proposed process and the substance to the society as a whole? This benefit could be enhancement of the public health, creation of jobs, enhancement of technology, or promotion of the economic health of the nation.

4. What are the benefits to the population at risk?

5. How do these risks, particularly those assumed by the population at risk, compare with comparable processes and substances? In the context of this assessment, there is no reason to exclude risks and benefits from existing processes and substances including those directly or indirectly derived from natural products and systems.

The processes outlined above (risk assessment, comparative risk assessment, risk-benefit assessment, and comparative risk benefit assessment) are essentially the domain of the scientific community. In contrast to these, the final evaluation of weighing these and coming to a management including regulatory decision is not a scientific process and should not be managed as such.

In the safety assessment of food, often a safety factor is used. This factor is arbitrary chosen to be 100. However, a properly performed risk assessment provides the most likely estimate for normal population and an estimate for those who are unique either in their physiological makeup or in their lifestyle, the latter causing excessive intake of a substance. There is no reason to rely upon an arbitrary factor.

The current testing for additives or processes no longer provides an acceptable method for food safety assessment. The current test methods to feed rodents exceedingly high levels of a substance and extrapolate to low levels in humans were based on the notion that one should be prudent in assessing a product. This approach is mechanistically incorrect. It disregards the biological repair process, a well established and well-documented biological system. The problem is aggravated by the practice of certain regulatory agencies to choose the upper 95th percentile of the extrapolated data rather than the most likely estimate.

The current system assumes that it is better to exclude 10 safe products if the chosen process leads to the exclusion of one unsafe product. This notion is based on the assumption that there is a sharp line between what is safe and what is unsafe. This is a false assumption. In the overwhelming majority of cases there is not a sharp line between what is safe and what is unsafe. The safety factor of 100 was an acknowledgment that such a sharp line does not exist. Essentially all products pose some risk and the task of the scientific community is to provide the decision maker with the most accurate level of that risk. The decision maker must weigh the risks and benefits and make an informed decision.

Another equally important problem with the notion underlying current practice is a disregard for benefits that the society may never reap. A properly managed food safety assessment program must include a risk assessment and risk benefit analysis for the lack of availability of the product under consideration. For
example, a process that is intended to extend the shelf life of a food must include a risk assessment of spoilage of food under normal and common practices that the product attempts to rectify.

Despite their shortcomings, the animal testing and extrapolation from rodent exposed to high doses to humans at low doses are necessary and are the foundation of toxicology and risk assessment. The opposition is not to animal testing or extrapolations, but to the method of extrapolation and particularly to the presentation of results and how they are applied.

Risk assessment must be as realistic and as accurate as scientifically feasible. The choice of extrapolation model (both from high doses to low doses and from animals to humans) becomes less significant if the model is routinely calibrated with food components currently in use. There is a great deal of knowledge on the composition of food. It is most likely that appropriate materials can be found in the currently accepted food for a comparative risk assessment, a powerful and heretofore unrecognized method for safety assessment of food additives.

There is an argument that, currently, risk assessment is in its infancy and its performance is so poor that a statistically validated risk assessment would have a large error bar. According to this argument, the decision point is well within the error bar, thus making the entire risk assessment useless. There are several problems with this argument. First, the nation is entitled to know the status of safety assessment and the basis for decision making. If the results of risk assessment are so uncertain as indicated by the above argument, the nation must be told that the regulator is making decisions absent of the necessary knowledge. Second, assumptions used for the risk assessment of a food additive are normally similar and often identical to those used for naturally occurring materials. Accordingly, during the comparative risk assessment, most uncertainties cancel each other out. In effect, an additive is compared to an existing and often widely used compound. Finally, this argument, if accepted, would negate the need to develop the only tool that is currently known for the quantitative scientific assessment of food safety. We need to recognize that a guessing game does not help and reliance upon emotions or ideology is not the proper tool for safety assessment of food. Eventually, the nation needs a rational and scientifically defensible method and must pay sufficient attention to the development of foundation of safety assessment.

The shortcomings of the current food safety management can be demonstrated in the following examples: It is known that raw egg on occasion may contain *salmonella*, the cause of significant harm including fatality. Similarly, raw oyster may contain harmful microorganisms. Food irradiation can be used to remedy both problems. Instead, the consumer is told either not to consume these items or take the risk. A similar situation exists with raw poultry. Although poultry is normally cooked prior to consumption, the cooking process can cross contaminate other foods.

The scientific disciplines required for the process outlined above are:

1. Toxicologist with sufficient training and experience in toxicity assessment of materials posing acute as well as chronic risks.

2. Nutritionist with sufficient training and experience to assess the nutritional need of various segment of the population.

3. Agricultural scientists and engineers with training and experience to indicate the consequences of changing a process or permitting (or banning) a food additive.

4. Process engineers with sufficient training and experience in the technology of food production.

5. Microbiologists with training and experience in the microbiology of food spoilage, its consequence and methods for avoiding them.
6. Chemists with training and experience in food analysis.

7. Economists with experience and training in cost benefit analysis, economic assessment of a process or a product and other issues related to food processing and agricultural economics.

8. Risk assessors with the needed experience and training to develop and apply models to combine information and provide useable information.

An important part of any properly managed risk is risk communication. The FDA along with other regulatory agencies must dedicate resources and intellectual commitment to this exceedingly important subject. The primary reason for the general lack of appreciation of the public for risk assessment and the politicization of risk assessment and cost-benefit analysis is the insufficient attention of regulatory agencies to risk communication.

Another hereto under-recognized resource is the role of professional societies in risk assessment and, to a lesser extent, in risk management. However, professional societies can play a crucial role in risk communication and should recognize their unique competency and credibility to perform this important task. I congratulate FASEB for undertaking the task of looking into food safety. I am confident that the results are likely to be more accurate and objective than other potential approaches.

In summary, I strongly recommend the application of risk analysis including risk assessment and risk-benefit assessment in the evaluation of food safety. An exceedingly powerful tool is the comparative risk assessment, comparing the risk of a proposed additive or a process with the existing materials and processes. It should be recognized that excluding a material or a process has a risk associated with it which should be compared with the risk of its usage. Regulatory agencies should devote more efforts to risk communication. Professional societies such as FASEB are uniquely qualified to assist regulatory agencies in these efforts. They have an important role in risk communication.
RESPONSE #2

Kirschman Associates
P.O. Box 88
403 Barrett Road
Emmaus, PA 18049

My apologies for this tardy response to your rather daunting request of November 3, 1995 for comments on food safety.

So much has already been said and written on this many faceted subject yet much yet needs to be done. With the time available I've been able simply to share with you here my observations on several points.

I commend this move by FDA to involve FASEB for further evaluation of food safety procedures. Scientific advances, data gathered and experience since enactment of the 1958 food additive amendment to the FD&C Act urgently warrant some changes in the way food safety is addressed.

I also think the FDA initiatives with Redbook I & II have been productive ventures in this scientific dialogue. The effort must continue until there has been an adequate level of agreement among food safety scientists and appropriate meshing then with regulations, including international harmonization on basic premises.

Here are some perspectives I've developed during my 35 years in the food safety arena.

A. Our food supply is quite safe. Its safety can be indexed by the observation reported by IFBC in Chapter 2 of their report (1). Only 209 toxicants have been documented (2,3,4) as a) causing adverse effects in human's in a normal diet (21+); b) or suspected of causing adverse effects in humans from atypical use, abnormal diet, drug use, substance abuse, or ignorance (93+); c) causing or suspected of causing adverse effects in domestic animals (84+); d) or suspected of causing adverse effects in experimental animals (161+).

Significant margins of safety of our food additives has also been assured by the analysis reported by Rulis (5)

References:


B. The purpose of our food control mechanisms, scientific and regulatory, should be oriented towards maintaining and improving, not diminishing, the adequacy (i.e. safety, wholesomeness and availability) of our food supply.
C. Just as the value of individual foods must be considered in relationship to their position in the entire diet, individual food components should also be evaluated with respect to their position in the food supply. Their contribution to the overall safety, wholesomeness and availability of our food supply should be part of their evaluation. The benefits of new foods and food ingredients must become part of the equation.

D. The advent of biotechnology and new foods, as well as food additives derived therefrom, bring focus, like nothing has before, to the need for "comparative safety assessment" (i.e. comparing the toxicity and safety index of proposed new products with the many foods already existing in the diet.) We no longer have the "luxury" of testing whole foods and macro-ingredients by feeding test animals >100 fold levels at which the component is to be found in human food.

E. Regardless of the type and number of toxicity tests that science might devise, the challenge of testing the estimated 200,000 food components, out of the 5,000,000 plus known (6) chemicals in our universe is prohibitive to consider at this point. Accordingly, and certainly in light of the relative safety of the food system shown above (4/), it would appear that traditional foods with which we've documented safe human usage, can confidently be used as the primary reference point. This would serve well, not only for whole new foods (e.g. biotech derived) but for macro and micro ingredients as well.

References:


F. The approach to the safety assessment and management of flavor use under the Generally Recognized As Safe (GRAS) concept has many aspects that could be considered for application to nature-identical and natural-like - in foods - materials beyond flavors.

The Consumption Ratio (7) relates the amount of a flavoring material found in natural and traditional foods to the amount added to food by food processors. This is then one step in the decision-tree approach to the evaluation of flavors in order to establish them as GRAS.(8).

References:


G. I do think some (e.g. acute, sub-chronic) animal feeding testing is needed for most new food materials. This is the only way to provide some overall comfort that one has "covered" all probable introductions of problem, not only from the chemical entity itself, but unexpected introductions of safety concerns by the manufacturing process (i.e. harvesting, synthesis, isolation, packaging and storage). However, I'm confident that we've gathered adequate data and experience to show that chronic feeding studies are not a necessity to assure the safety of food additives. Use of known chemical structure activity relationships (SAR), natural occurrence of the same and similar materials already in our foods, metabolic disposition and body burden similarities to "safe" food components, all in a coherent decision tree approach (8) should provide more assurance of safety than has been provided over the past 25 years by chronic feeding at the MTD. More prudent use of 90 day feeding study data would have done a better job on this.
H. Any "carcinogenicity" data used in the structure activity evaluation should be well grounded in more recent 1990's weight of evidence criteria. Indeed, Dr. Haseman of the NIEHS stated (9) "In particular, a decision rule that routinely labels a carcinogen whenever a single tumor increase is significant at the 5% level for any exposed group can result in a false positive rate considerably greater than the nominal 5%." He went on to say, "also, statistical decision rules should not be employed as a substitute for sound judgement in the overall evaluation of these experiments."

References:


I. Since humans are the primary subject of our concern and chemistry, in-vitro testing, and testing in surrogates cannot tell all, some premarket exposure and limited testing in humans, as well as close post-market surveillance (e.g. follow product complaints) is warranted.

References:


J. Once the professional community comes to agreement on the updated procedure to be used for regulation and assuring the public of the safety of its foods, continuing efforts must be undertaken to educate the public about the Facts On Food Safety.

I do hope you and your colleagues find this commentary of some value in your deliberations. If so I'm pleased to have been of some help.
RESPONSE #3

Michael A. Kamrin, Ph.D.
Professor
Institute for Environmental Toxicology
Michigan State University C-231 Holden Hall
East Lansing, MI 48824-1206

A number of current risk assessment efforts, such as attempts at risk harmonization in the U.S. and the President's Commission on Risk Assessment and Risk Management, reflect a dissatisfaction on the part of scientists and others about the way that science is used in assessing risk. In my view, one main impetus for these efforts is the belated realization by scientists that current risk assessment procedures, particularly those developed by EPA, are purported to be scientific but are really almost entirely policy based. Decisions as to which data sets are to be used, which data points will be selected, how positive and negative results are to be combined and interpreted, and how extrapolations are to be made from laboratory animals to humans are all policy based and have the underlying goals of consistency and prudence as opposed to fidelity to science.

In essence, current regulatory approaches attempt to manage risks without understanding them and, in most cases, ignore a significant amount of scientific information that can contribute to understanding because these data are not available for all chemicals or because there is no simple formula that can be used to incorporate these data into the assessment process. The result is that chemicals with very different properties are assessed similarly; e.g., genotoxic and non-genotoxic carcinogens. This leads to management strategies that may overestimate risks of some chemicals and underestimate risks of others; both results have the potential to be detrimental to overall public health.

My response, and one that I think is shared by much of the scientific community, is that all relevant scientific information should be used in evaluating risks. I do not believe this can be done by proscribing any particular set of studies or criteria in the evaluation of toxicity. Understanding in science is achieved by many routes, not by the application of rote formula.

It may be possible to define the end product of the risk evaluation but this should be done in broad terms such as those used in the legislation: "reasonable certainty in the minds of competent scientists". It is not appropriate to specify that, for example, immunotoxicity tests X, Y and Z and neurotoxicity tests A, B and C need to be performed. While they may be appropriate in some cases, they may not be needed in others; this is a matter of scientific judgement.

The first question posed by the FDA (in the enclosed attachment) provides an example of a situation where proscriptive batteries of tests may not be appropriate. If a chemical that naturally occurs in some foods is added to other foods in quantities that do not appreciably increase overall intake, are such tests batteries needed? Perhaps not in this case; rather the most appropriate testing would be to determine if the addition of this chemical to a new food results in any difference in the toxicokinetics or toxicodynamics of this compound. If not, then additional testing does not seem warranted.

Indeed, in general, if there is a body of scientific evidence available that indicates that the toxicokinetics and/or toxicodynamics of a chemical in humans is quite different than that in experimental animals, then requiring a battery of tests on this chemical in experimental animals may not be appropriate. Instead, data relating to the metabolites and/or target organs in humans would be more appropriate. Using this approach, it may be found that chemicals that test negative in proscribed animal tests are not safe for humans at expected exposure levels or that chemicals that test positive are safe at such levels. In either event, more complete scientific information provides a more appropriate conclusion.
There are many other types of scientific information that might be appropriate in specific cases; e.g., the transformations that might occur during cooking or interactions that may happen when foods that commonly used together are combined. In addition, there are situations where it is not really a chemical but a whole food that is of concern and for which standard tests are even more inappropriate. As these examples illustrate, it is not possible to predict beforehand all of the possible types of scientific data that might bear on the risk from a particular food or food component.

Thus, I do not believe that there is any way to arrive at a unique set of criteria that can be used universally to answer risk questions such as exactly what an adverse effect is, or how to determine if an adverse effect in animals is applicable to humans. If this is the case, then expending great efforts to reach consensus on such criteria is not likely to lead to the desired result; a scientifically sound approach to the assessment of risk from foods.

What is the alternative? I believe that the most scientifically appropriate way to make a judgement is to bring together those scientists most knowledgeable about the particular situation in question; e.g., the chemical and/or food of concern, and have them arrive at a consensus as to whether the utilization of this chemical at a particular level is likely to cause harm. If these scientists cannot agree, they can provide recommendations as to additional information that is needed to resolve remaining questions. Similarly, if they decide that the available information is not sufficient to make a determination they can recommend exactly what information will be required before a determination can be made.

While the consensus of the scientific panel can only be a recommendation to the FDA, it should be understood that the agency would be expected to follow the recommendation unless some compelling reason to negate the panel conclusion is provided. Also, while the FDA is responsible for making the decision, it would seem likely that those commercial interests which intend to propose new additives will employ a similar panel to minimize the possibility of developing a product that will not be approved.

It might also be appropriate in the case of a product that the company evaluates positively, that the FDA have the option of accepting the report of the panel hired by the commercial interest or convening a new panel. This might encourage the best use of science at the earliest stages of development.

Having spoken with chemical industry representatives, I know that one of the problems they see with government expert panels is that they cannot predict the result and so have trouble planning ahead. They feel that the current system which utilizes a set of known criteria and methods minimizes this unpredictability. However, I do not feel that this concern is warranted based on the extensive experience I have had working with expert panels. In such situations, I have found that when there is sufficient evidence available there is not much unpredictability in the result. I also feel that the benefits to society of better use of science should have a higher value than predictability of results.

One additional concern that I have is that the regulation of chemicals in food be done with the recognition that these same chemicals may be regulated differently in other media; e.g., water or air. The promulgation of different acceptable intakes by a number of agencies with different regulatory responsibilities can undermine the faith of the public in the actions of any or all of these agencies. As one who spends a lot of time communicating risks to the public, such inconsistencies are a significant roadblock in helping citizens make individual decisions about chemical risks that they may face.

Thank you for the opportunity to provide input to the FASEB Expert Panel. If you would like me to amplify on any of the points that I have made or provide any additional information, please don't hesitate to contact me.
RESPONSE #4

Andrew G. Ebert, Ph.D.
Executive Director
International Food Additives Council
5775 Peachtree-Dunwoody Road
Suite 550-G
Atlanta, GA 30342

In November, 1995, FASEB, as part of a contract with FDA, solicited comments from experts and interested parties in the area of food safety evaluation on the process of establishing consensus for required criteria needed in the determining the safety of new food ingredients.

Although the views of IFAC were not specifically sought, IFAC staff and member company scientists have considerable experience in this field. As we therefore have a number of pertinent view on the topic, we send them to LSRO with the request they be added to the comments received and sent to the Expert Panel for use in their deliberations.

(P.S. IFAC staff has addressed a number of the points raised by LSRO. A copy of a book chapter published in 1989 which looks at some of these issues is attached.)

I. Strengths and Weaknesses of the Current Scientific Aspects of Food Safety Evaluation.

1. Perhaps the greatest strength of current methods is the fact that they are used as part of a system based on animal models, which has evolved over the years for the toxicological evaluation of many substances. It has basically served well. The evidence of morbidity and mortality from the use of intentional or unintentional food additives and their ingestion is vanishingly small, far lower, for example, from the inadvertent ingestion of microbiological hazards present in food due to improper preparation or handling.

2. Although the basic system of toxicological evaluation has worked well, its inherent characteristics best reveal toxic manifestations following short term exposure of relatively large amounts of toxicant e.g., drugs, whereas food additives may be ingested at low levels for prolonged periods, perhaps a lifetime, by humans. Therefore there is little room for error. There is a tendency to grossly overload animal model systems in an attempt to extrapolate toxic manifestations to longer administration of lower doses. The problem thereby created, however, is that these tests often use rates and routes of administration that at worst are outlandish and at best have little relevance to the intended mode of use of the food additive of interest.

3. As described later in this letter, emerging food additives include macrobiotics whose initial and perhaps prime toxicological manifestation would be modification of some nutrient aspect of the food to which added. It may therefore be necessary to amend toxicological testing accordingly.

II. Proposed Changes in the Criteria for Safety Evaluation

1. One basic change proposed by IFAC scientists calls for the reintroduction, by FDA, of the concept of "concern level" proposed in earlier revisions of FDA's "Redbook." Chemical and physical properties of new food additives in comparison to the biological activity of substances previously evaluated as well as the amount and duration of exposure should become major factors in designing food additive safety evaluation programs. We believe this current "Redbook" fails to take these important basic factors into consideration.
2. Greater significance should be given to biological and food technological aspects. All potential applications for a given food additive in amounts reasonably anticipated to be ingested should be considered. Moreover, the fate of the substance when added to food and in those persons consuming that food should strongly influence the types of toxicological studies to be carried out. An obvious example would be detailed studies of the effects of a fat substitute on all aspects of fat metabolism and the nutritive impact that fat substitutes might create. With such a food additive, the experience of food technologists and nutritionists would be of value in assisting toxicologists in the design of appropriate safety evaluation studies.

3. Although an accepted part of the clinical evaluation of therapeutic agents, human studies have not routinely been part of food additive evaluation. Given that a good part of new food additives may be in the form of macronutrients, there appears to be an increasing need for limited but well designed and carefully controlled studies in humans.

4. The value of ARM and other anecdotal reports from the field without appropriate and careful follow up appears to be nil. In this age of quick and easy communication, it is easy to convey the view that a given substance is the cause of ills, real or imagined, by the person reporting, but a way to follow up and evaluate the quality of their anecdotal reports is almost always absent.

III. **Rational and Circumstances When Changes Would be Required.**

1. Two major factors could be expected to impact upon circumstances requiring a new approach in toxicological evaluation. The first is in food science, the second is in toxicology.

In food science, the change from more traditional foods to specialty foods with defined intended effects (sports drinks, caloric supplements, nutraceuticals are examples) continues. Desire of the consumer to "pop" a specialty food such as they might previously have "popped" a "pill" appears to be growing. Regulators and the regulated industry will want to determine, with the greatest possible accuracy, patterns of use of a new food additive with particular reference to those who might consume the additive in unusually high amounts or for prolonged periods. Market basket surveys will now have to be linked to production figures. Those who engage in the sale of food additives could well be required to track with a higher degree of accuracy the food in which the food additive of interest is applied.

In toxicology, there are strong pressures to move toward studies in model systems of animal cell types, i.e., not involving intact animal systems. Food safety evaluation in non animal test systems could be expected to follow once it has been assured that the use of alternatives to animal testing provides a reliable predictor of effects in humans.

2. The LSRO document seeks comments on the matter of new approaches. If there are to be new approaches to toxicological testing, there will have to be a change in attitude on the part of regulatory agencies. Scientific methodology is slow to change. Because the development of new methods proceeds at a very slow pace, there is every reason to believe that existing animal model systems will remain the mainstay of safety evaluations of food additives even as toxicological testing using non animal systems continues to be developed.
RESPONSE #5

Kenneth D. Fisher, PH.D.
K D Consultants
17815 Mill Creek Drive
Rockville, MD 20855-1020

This letter is in response to your request dated November 3, 1995 for comments on the process of establishing a scientific consensus on criteria required to determine safety of new food ingredients. First, my apologies for the tardiness of the response, but now that I am a consultant, I have adopted the typical consultant’s habit of less than optimum punctuality. My comments and thoughts on the issues are contained in the following paragraphs.

In regard to the process being used by the LSRO to respond to FDA’s task order, I suggest that your initial panel of experts draft a background paper from the comments received as you indicated. However, I would suggest that the comments in their totality would be a useful appendix to that document. If persons object to being identified in such an appendix, the individual letters could be redone blind. I, for one, have no objection to my letter being made public with one caveat. That is, the contents of this letter represent my own thoughts based on 30 years of experience in the evaluation of food safety and related issues. They are not related to, nor are they to be misconstrued as the opinion of any organization, public or private, for which I am currently consulting.

In a general sense, much has been written on the past several decades concerning safety of substances, be they food ingredients, drugs, environmental contaminants, etc. Reports of the NAS/NRC on chemicals in the environment, the Food Safety Council’s reports, several LSRO reports, the FDA Redbooks, Lowrance’s “Of Acceptable Risk”, Dick Hall’s decision tree approach, and many other documents are quite instructive in regard to criteria for safety evaluation and suggested guidelines on interpretation of data. My point is that it is not necessary to reinvent the safety wheel. The information to undergird a system of acceptable criteria and interpretive guidelines are available and are, in general, in use, albeit in a less that satisfactory and acceptable framework. Major aspect of this dilemma is that the criteria don’t change but the interpretation does. LSRO should document these important references as a part of its Background Document, indicating which parts of each are pertinent to criteria and to interpretation.

1. Strengths and weaknesses of the current scientific aspects of food safety evaluation.

It is absolutely essential to separate the current debate on food safety evaluation into two distinct issues. One is the scientific criteria; the other is the FDA process of evaluation. The former issue is the task for LSRO; the latter task is currently, and I suspect will be for a long time, a matter being addressed by Congress. Somehow Congress and especially the legal community, need to be aware that their job is to address the system and process, but leave the matter of scientific criteria to the scientific community. This will not be an easy or straightforward task as the two issues have been obscured by both the scientific and legal communities for a number of years.

Second, one has difficulty assessing the strengths and weaknesses of the current scientific aspects because the process of evaluation is unclear. The Redbook provides guidelines but few criteria or interpretive guidelines; FDA papers and talks indicate what and how they evaluate safety, but rarely identify what criteria, cutoff points, statistical and/or biological significance levels are used in the decision-making process. What are the criteria in use? Can FDA state what they were in 1980, 1985, 1990, and 1995? Is there some way that FDA might summarize how the criteria have changed or remained the same over time? I have seen the “template” but that is a “process” document; is there a written set of interpretive guidelines for each of the criteria in use today? Only FDA knows. Perhaps one way to clarify this matter is to ask FDA to brief the Expert Panel on the details of two of three
safety evaluations; e.g. a simple one, and one or two complex ones done in 1990 or 1985, and a similar set done in 1994-95. In defense of FDA, they have a tough job because they must publish decisions (a point in time) yet scientific studies and consensus on criteria and their interpretation are dynamic and constantly evolving.

It is somewhat ironic that the guideline of 1/100 as a general safety standard has served the American public well for several decades, yet now reasonable certainty of no harm is a standard being interpreted by the courts. In the basic sense, reasonable certainty is defined as an acceptable value judgment by experts qualified by training and experience to make such decisions. Until recent years, these decisions were solely in the scientific arena; now they are not. Within the scientific community there is considerable discussion (noise, flax, harping, carping, disagreement) on what constitutes qualified, training, experience, etc. This open, continuing discussion within the scientific community has led to the public disenchantment with science and they have sought other avenues of resolution, e.g. the courts. This has affected FDA (and EPA as well) by the lessening of the reliance on scientific aspects of the evaluation process and a rising reliance on non-scientific aspects, i.e. the process rather than the substance. This leads me to observe that the LSRO effort, and any others in the future, will probably never resolve the issues associated with scientific aspects of the process of food safety evaluation. It follows that what can be done is to:

a) state the current consensus on what criteria should be, i.e. chemistry of the substance, method of manufacture, composition, possible exposure estimates, in vitro or microbial studies of metabolism, acute and chronic studies in two species of laboratory animals (if not necessary state why), and human studies (again, if not necessary or possible, state why).

b) provide interpretive guidelines for each of the criteria.

c) suggest a schedule for re-review and updating and a mechanism to do so.

d) make these publicly available.

What I am suggesting is that science say what it can and cannot do; the scientific community by itself can only contribute to the ongoing dialogue; it cannot resolve the majority of the issues because the public is unwilling or unable to let science do so. In a sense, scientific criteria for food safety evaluation, once stated succinctly, will be much like the “cure for cancer in 20 years”; outdated when published and impossible to meet without modification.

2. Proposed changes in the criteria - - - - - of new approaches).

As evidenced by the above paragraphs, my concept of criteria and their interpretation in regard to food safety evaluation is relatively traditional. If it ain't broke, don't fix it. However, there are two disciplinary areas where new or improved criteria are needed. These include neurobiology and immunology. Specifically, there is a need for predictive test of neurobiological and immunological consequences of ingestion of food substances. Such tests are now available; but, criteria for their interpretation are woefully lacking. For example, we know certain amino acids affect discrete brain functions. Are the effects transient? How long? What is the dose response? Do the transient effects have long-term secondary sequelae? If a new food ingredient is an amino acid or a derivative thereof, what do these neurological effects mean when compared to foods containing that substance, other amino acids with similar metabolic effects, other derivatives, etc.? Resolution of this need is almost entirely dependent on basic and applied research, research that is yet to be done. We need to state so, and indicate that science can address these issues if the research is done; if not supported, science can only report but not interpret the date.
In an analogous manner, immunological consequences of consumption of new or improved food ingredients (and for that matter, new foods) are known to some degree, but again, the ability to interpret data is seriously compromised by lack of adequate research.

3) Rationale and circumstances when ------- will require a new approach.

There are three areas where the need for improvement in the scientific aspects of food safety evaluation might be made in the near future. These are: 1) the matter of additional uses for a substance already approved; 2) new ingredients closely related to the chemistry of an already approved substance; and 3) the matter of macronutrient substitutes.

To some extent, I suspect that FDA already does accomplish #1 and #2 by some informal means. The decision on a new food ingredient could be prepared before the fact, or after the fact, in a manner so as to provide a description of the criteria used, their interpretation, and possible additional data needs if similar or related substances are advanced by petition. In the case of new uses (#1), the petitioner and those who might object should be put on notice that they must supply data that suggests a reasonable added exposure estimate and any scientific studies that extent the extant knowledge base about that substance. In the second scenario (#2), the secondary petitioners, and those who might object to approval of substances based on criteria and interpretations upon which approval of the first such substance were made, should be put on notice that they must meet the data standards determined adequate for the first substance (i.e. the subsequent petitioners), or that they must provide data or reasoned explanations of what was lacking in the first approval and what is needed additionally for the subsequent substances approvals. The matter of proprietary data might be an issue; but in my view, it could be resolved by legislation analogous to that in the Orphan Drug Act; i.e. exclusivity and royalties. Nevertheless, some formalization of the guidelines on criteria and decisions on interpretation made public or available on request, would be useful.

In regard to macronutrient substitutes, the issues are a bit more difficult. I suspect this topic is the one that spurred FDA to ask question #1 on the Enclosure with your letter of November 3, 1995.

One can presume that a macronutrient substitute will have chemical and physical characteristics that provide some information on both safety and toxicity. Such data would be expected from initial studies of the substance by the petitioner. These should be useful in prediction of the type and extent of additional studies needed. There are no firm answers to whether one or more animal feeding trials are necessary. The recent experience with Olestra is instructive. Indeed Olestra could be used as a good example by the LSRO Panel in its effort to develop a set of guidelines on the extent of testing needed. An in-depth analysis of why P & G did each study, i.e. what prompted the study, as well as a critical review of the reasons why FDA relied on some studies and gave less “weight” to others done by and for P & G might be a logical way to approach the issues related to macronutrient substitutes. Experience with substances such as modified carageenans (natural), guar gum (natural), capremin (synthetic), and salatrin (synthetic) seem to indicate that some animal testing is necessary prior to human testing. In each case, human feeding trials proved to be essential. The issues about the human feeding trials were the classical ones, dose and time of exposure. Perhaps guidelines on dosages (1X, 2.5X, 5X) and length of feeding would help standardize such studies. Clearly 5 to 7 days is not sufficient; but, 1 to 3 months might be cost prohibitive. Olestra is probably the best and worst example; why not learn form the experience by critical analysis.

Finally, the issue of third party review of petitions needs to be addressed. Congress is inching up on legislation that will include third party review of food ingredient petitions; but these efforts, as usual, are focused on the process, not the substance. If third party review is to succeed, it must be science-based. If it is to succeed, then those organizations and individuals must all use the same set of scientific criteria. A goal of the LSRO effort should be to provide FDA, and the third party reviewer community with a set of criteria,
guidelines, etc. with a reasonable set of these. One issue to be addressed in FDA is the problem of different standards for additives, GRAS ingredients, supplements, etc. A second issue is the need to avoid the rigid approach of EPA used for pesticides, etc. There is no mathematical model for all substances yet; similarly, there are safety factors which, while used for years, have an increasing number of exceptions as science learns more and more about nutrition, cell metabolism, and metabolic responses to ingested substances.

This appears to be a rambling discourse, which it is because the subject matter is quite vast. Hopefully, LSRO staff will be able to take the comments here and from others, and develop a schema, progression, or decision tree approach that allows decisions to be made sequentially, building on each previous decision.

If any of the above comments require additional discussion, let me know. If I can be of further assistance in the future, please contact me.
RESPONSE #6

Fred H. Degnan  
King & Spaulding  
1730 Pennsylvania Avenue, NW  
Washington, DC 20006-4706

Thank you for your letter dated November 3, 1995 asking for my thoughts and views on a number of questions related to FDA's evaluation of food safety. Although the questions as designed more for scientific rather than legal input, it is prudent that FASEB has solicited the views of lawyers engaged in the practice of food law because, for better or for worse, the law provides the standards by which the value of scientific data and the informed expert opinion resulting therefrom is measured. As a result, the process FDA follows in making food safety determinations is not wholly scientific. In fact, the process is distinct from the fundamental scientific process of consensus gathering because the law often forces FDA to make a science-based decision on a matter about which there may be no true scientific consensus.

Another important preliminary consideration related to your inquiry involves the fact that the regulatory authority FDA relies upon to ensure the safety of food reflects the diversity of the food supply. In particular, the Federal Food, Drug and Cosmetic Act ("the Act") contains a variety of standards for the regulation of food safety. The Act, however, does not amount to irrational public policy. Although perhaps open to questions by today's scientific standards, the diversity of the Act in handling distinct types of substances and ingredients reflects fairly consistent congressional efforts to provide comprehensive, practical public health protection.

It is not surprising that, under such a regulatory scheme, developments from time to time in modern science have called into question the empirical underpinnings of an aspect of the agency's regulatory authority. The upshot is clear: food regulatory safety issues have the potential to involve a real tension between the dictates of science and the prevailing interpretation of statutory authority. It should also not be surprising that developments in science have, with some regularity, forced the agency to interpret and apply its regulatory authority in ways never contemplated by Congress. Simply put, any assessment of FDA's food safety decisionmaking must be grounded in the appreciation that food safety decisions are often the result of an amalgam of legal, scientific and policy considerations.

Your letter focuses particularly on FDA's evaluation of the safety of intentional food ingredients -- "food additives." As you know, the legal rubric for evaluation the safety of such ingredients was established in 1958 with the passage of the Food Additives Amendment were: (1) safety -- "to protect the health of consumers" by requiring manufacturers of food additives to "pre-test potentially unsafe substances added to food" and (2) innovation -- "to advance food technology by permitting the use of food additives at safe levels." These dual goals of safety and innovation are achieved, in part, through a system of premarket approval that subjects substances satisfying the statutory definition of "food additive" to a rigorous but practical and non-absolute safety standard.

Congress did not define "safety" in the statute, but explained in legislative history that the manufacturer's burden to prove safety would be met upon presentation of evidence establishing to FDA's satisfaction a "reasonable certainty" that "no harm" would result from the intended use of the additive. For your purposes it is important to note that Congress expressly acknowledged in passing the Food Additive Amendments that safety (other than for substances "found" to "induce cancer") is dose dependent (i.e., that substances toxic at

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2 Id. at 4
high doses might be safe at low doses) and that proof of absolute safety under all circumstances is a scientific impossibility.³

In short, in developing the food additive approval rubric Congress sought to ensure safety and advance food technology by permitting the reasonable exercise of sound scientific judgment concerning the safety of food ingredients. Congress also sought to balance safety with the practical needs of not disrupting the food supply and knowledgeably allocating scientific and regulatory resources. Balance was, in part, achieved through the definition of the term "food additive" by excluding from the definition and, thus, from premarket approval schemes accompanying such additives, substances that are generally recognized as safe, i.e., "GRAS." Balance was also ensured by the implicit recognition that sound scientific judgment as to what constitutes "safety" would be applied to the decisionmaking required by the Amendment.

The fact that FDA's food additive and ingredient regulatory approval system does not demand absolute safety is fundamental to efficient science-based agency decisionmaking. As mentioned at the outset, the regulatory arena does not have the luxury of waiting for scientific consensus to develop on a given issue. FDA must act on the basis of the information before it. For this reason the agency's own definition of "safety," now codified at 21 C.F.R. § 170.3(h)(i), qualifies the reasonable certainty of no harm standard with the following acknowledgment: "It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance."

Implicit in this acknowledgment is the recognition that any agency failure to focus on the need for judgment in exercising safety decision has the potential to result in the paralysis of food safety decisionmaking. This recognition leads to a fundamental issue with which you letter is concerned: the nature of FDA decisionmaking regarding the safety of food ingredients.

Precisely because absolute harmlessness can never be established and because the law recognizes this truism, FDA's decisionmaking processes regarding food safety would be greatly enhanced if the agency's unique regulatory science role is clearly distinguished from the role of pure scientific inquiry. The legal system neither contemplates nor can afford asking and answering every possible scientific question presented by the use of a food ingredient. the real challenge for FDA (and for the scientific community) is to ask for and identify those studies regarding an aspect of the safety of an ingredient which are likely to add some real value to the food safety decisionmaking process. The Center's recent procedures and criteria for evaluating the safety of food products of transgenic plants reflect a successful response to this challenge.

Where a test or additional layer of review is unlikely to have any meaningful impact on the ultimate decision of safety, imposing the conduct of such a test or review as a condition of premarket approval is wrong. The law is clear: not every scientific question must be answered before a substance is approved as safe for use in food. A heavy burden, thus inexorably falls on the regulatory scientist to use his or her most informed judgment in evaluating the safety of an ingredient and to limit a possibly unending array of questions to those that are most likely to shed light on a consideration relevant to establishing whether the use of a food additive

³ The House Committee primarily responsible for developing the Food Additives Amendment stated in its report on the bill:

Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not -- and cannot -- require proof beyond any possible doubt that no harm will result under any conceivable circumstance... The scientists pointed out that it is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of any chemical substance... Reasonable certainty determined in this fashion that an additive will be safe, will protect the public health from harm and will permit sound progress in food technology. Id. at 4-5.
presents a reasonable certainty of no harm. This freedom to use scientific judgment and to accept some degree of uncertainty in decision making eschews exclusive reliance on cookbook or recipe-type data requirements and is essential if the regulatory goals Congress set -- goals that do not precisely correspond to the goals of pure science -- are to be met. Agency scientist, thus, must be encouraged to use their scientific judgment and the scientific community as a whole should be cautioned to evaluate such decisionmaking in the regulatory context in which it is made. The admirable, desirable goals of safety and innovation can be assured if such balance is struck.

Thank you for soliciting my views.
RESPONSE #7

Myron Solberg, Ph.D.
Professor of Food Science
Director, Center for Advanced Food Technology
Cook College
N.J. Agricultural Experiment Station
Rutgers University
P.O. Box 231
New Brunswick, NJ 08903

First, I want to thank you for providing the opportunity to enter my concepts and ideas in response to your request for comments and opinions relative to criteria required to establish safety decisions about new ingredients. I offer the following thoughts.

The first principle which needs to be considered is that advances in science combined with advances in the power to computers have established an opportunity for the utilization of modeling which was not previously available. Good chemistry combined with good models for process effects, digestion effects, metabolic, effects, nutritional effects, toxicological effects, and even unique effects such as illness or disease can provide very strong cases for ingredient safety. There exists a sizeable literature which could be incorporated into the development of the previously mentioned models. The areas in which the knowledge base become questionable can be identified and a research thrust can be developed to close the gaps. The models need to be continually improved as new research provides new knowledge. Failure of the model to provide a definitive answer would provide the option for the use of other approaches which may be the traditional ones of the present.

The second principle is that every ingredient should be considered individually. With good chemistry and a good model this can be readily accomplished. The Safety Assessment of Novel Foods guidelines prepared by ILSI Europe's Novel Food Task Force in 1995 has initiated some movement in the direction suggested above. In addition very serious consideration should be given to the very broadest application of the concept proposed in which a traditional food, accepted as safe, is used as a reference for a new food. Had such an approach been taken with respect to irradiated foods, the level of confusion would have been dramatically reduced and the safety of the public would have been dramatically reduced and the safety of the public would have been significantly improved. The need for good chemistry is very important in such an approach.

The model described above could take into account expected use levels, proportion of diet, reliance upon the food as a specific nutrient source, nutritional or health status of consumer, and other factors which may be considered important.

Although these comments are relatively brief, I feel that the take-home message which I would like to provide is that full advantage needs to be taken of the powerful new technologies which provide the science and the interpretative capacity to solve problems in new and efficient ways.

I hope these comments prove useful to you as you seek to provide meaningful input to assist the FDA in their evaluations of food safety.
RESPONSE #8

Yoshi-hisa Sugita, Ph.D.
Executive Director, Globalization Program
International Life Sciences Institute
1126 Sixteenth Street, NW
Washington, DC 20037-4810

Thank you for your inquiry dated November 3, 1995. I am honored by your letter and the solicitation of comment.

Safety evaluation of foods and food ingredients are the prime interest of ILSI. Technical Committees in many branches had addressed this issue. For example, at ILSI North America, Technical Committee on Macronutrient Substitution and Technical Committee on Food Components for Health Promotion and others addressed the issue. They published their findings and recommendations and submitted to relevant government agencies.

The International Life Sciences Institute is a non-profit, worldwide foundation established in 1978 to advance the understanding of scientific issues related to nutrition, food safety, toxicology and the environment. By bringing together scientists from academia, government, industry, and the public sector, ILSI seeks a balanced approach to solving problems with broad implications for the public's well-being. ILSI is affiliated with the World Health Organization as a nongovernmental organization and has specialized consultative status with Food and Agriculture Organization of the United Nations.

Through its international network of branches in Argentina, Australasia, Brazil, Europe, Japan, Korea, Mexico, North America, Southeast Asia, Thailand and a Focal point in China, ILSI works toward global harmonization by helping to solve scientific problems that touch people in many countries and regions. To fulfill their goal, the branches sponsor scientific research, conferences, workshops, symposia and publications.

To contribute to your questions as ILSI world wide, we may need more time and the deadline seems to be too short. I am forwarding you, at this moment, some of the relevant ILSI reports on these topics as well as a bibliography of additional references. Copies of these references are available upon your request.

Thank you again for giving us the opportunity to comment.

References:


12. ILSI Japan, Food Produced by New Biotechnology, Case Study on the Benefits, Safety and Public Acceptance of the Foods, Kenpakusha, Tokyo, Japan (1994)
Ib Knudsen, D.V.M.
Institute of Toxicology
Division of Nutrition
National Food Agency of Denmark
Ministry of Health
Morkhøj Bygade 19
DK 2860 Soborg, DENMARK

Our views and comments on the process of establishing a scientific consensus on the criteria required to establish safety decisions about new food ingredients

1. Strength and weaknesses of the current scientific aspects of food safety evaluation.

We agree to the statement in the OECD-report from 1993 regarding the concept of food safety:

"The safety of food for human consumption is based on the concept that there should be a reasonable certainty that no harm will result from intended uses under the anticipated condition of consumption. Historically food prepared and used in traditional ways have been considered to be safe on the basis of long-term experience, even though they may have contained natural toxicants or anti-nutritional substances. In principle food has been presumed to be safe unless a significant hazard was identified."

In the objective sense one has to admit that the present accept of foods and food ingredients is not science based, and no scientific tradition on how to perform a safety evaluation has been developed for general application to foods and thereby to novel foods. In specific areas regarding irradiated foods and single cell proteins and approach has been developed basically within FAO/WHO applying the pioneering work of Protein Advisory Group in the early 70'ties. The experiences gained in these areas provide now the stepstone for entering the scientific part of a novel food safety assessment era. If successful the scientific development in this field might provide - sometime in the future - the sound basis for assessing the scientific validity of the statement made by Petö and Doll in the early 1980'ties that 35% (10-70%) of cancer death in Americans have the diet and dietary habits as the dominating cause. If very successful the novel food testing may form the future scientific basis for new dietary advices to the American public. The present dietary advices which to a certain extent are based upon those hypotheses and not turned down in human epidemiological studies, may be replaced by human and experimental studies identifying the casual links between exposure and disease or absence of disease. If less successful the safety assessment of novel foods may keep away additional dietary threats to human health. If not successful at all "wild shots" in the development of novel foods may lead to a new generation of dietary induced diseases in the Americans.

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4 The opinions expressed here are those of the authors and are not necessarily those of the National Food Agency of Denmark.
2. Proposed changes in the criteria for safety evaluation.

We propose to introduce a stepwise assessment of the safety of novel foods. The first step in our approach is the assessment of possible substantial equivalence based upon information regarding the origin, composition and dietary intake of the novel food. The second step should encompass the assessment of substantial equivalence except for one or more defined traits (new traits and/or secondary compositional changes). If marketing is not accepted from step one or step two, the novel food may proceed to step three, where the assessment is based upon the total novelty of the food or food ingredient. Information requirements on the third step need to include animal studies, in vitro studies and human studies. Marketing of the novel food from either of three steps is followed through regular marketing surveys assuring that the overall role of the novel foods in the diet corresponds to the provisions given in the marketing licenses.

Step 1: At this step emphasis is focused on the assessment of possible substantial equivalence. It is important to keep in mind that the establishment of substantial equivalence between a novel food product and its traditional counterpart is limited to imply:

- that the safety - or unsafety - of the novel food to human health is equal to it unmodified counterpart,

- that when the conventional food product has a history of safe use, the analogous new product can only be considered safe to the same extent,

- that the establishment of substantial equivalence in itself is not equal to establishing the safety of the food as such.

It is also important to remember that if substantial equivalence cannot be established, this does not in itself indicate potential health problems connected with the new product.

The analytical parameters to be included in the assessment of substantial equivalence depend upon the novel food in question, whether it is of plant, animal or microbial origin. Although the focus will be on the novel food itself, the information to establishing substantial equivalence needs to relate also to the plant of origin, animal of origin, microorganism of origin to broadening the scientific validity of the analysis. The focal point for the comparison will primarily be the parent organism, secondly the species in a broader sense.

For plants the establishment of substantial equivalence does rely on such data as correct botanical classification, molecular characteristics (DNA-source, DNA-function, DNA-sequence data), agronomic traits (morphology, growth, yield, disease resistance, specific traits), critical nutrients (protein, fat, carbohydrates, ash, vitamins, minerals, others) and critical toxicants (inherent toxicants, contaminants). Also information regarding m-RNA analysis, metabolic profile, genotoxicity and cytotoxicity may provide useful information for the establishment of substantial equivalence.

For animals including both vertebræ and invertebræ, the correct zoological classification is important for assessment. Also information regarding molecular characterisation, morphological and phenotypical appearance, potential inherent toxicants as well as specific biological features is essential to assessing substantial equivalence.

For microorganisms the quality of the assessment depends upon the correct identification of the culture strain down to species and strain level. Also the purity of the culture needs to be documented through relevant microbiological tests. The information needed does include comparison of the culture strain to recognized type culture collection strains with respect to morphology, DNA- and RNA-profiles, enzyme profiles, secondary metabolites (inherent antibiotics and toxicants), plasmids and phag-types. Also information
regarding gut colonising abilities and infective properties as well as pathogenic potentials in mammals are integrated characteristics of the overall establishment of substantial equivalence.

For novel processes, information considered should include technical features of the process, critical chemical changes in the food, and changes in critical nutrients such as proteins, fats, carbohydrates, ash, vitamins, minerals, and others. Also information on critical toxicants not destroyed or actually formed in the product during the process, metabolic profile of the processed product as well as changes in genotoxicity and cytotoxicity induced by the process in comparison with a traditionally treated product is essential for the assessment.

Step 2: If substantial equivalence to a conventional food can be established except for certain defined trait(s), this or these trait(s) will be in the focus of the further assessment of wholesomeness. Based on the information given the specific properties of the traits are considered with respect to nutritional properties and toxicity. The assessment will have to take into account previous experiences regarding such constituents, their natural food occurrence and their possible future role in the overall diet. For novel traits with no previous or natural food occurrence, no previous use as food additives and no toxicological data, a full data package as the one for food additives may be needed for the assessment. The wholesomeness assessment should take into account the chemical nature of the new trait(s) in question as well as the expected level(s) in the novel food as marketed and the envisaged role of this novel food in the diet.

Step 3: For those novel foods, where no substantial equivalence can be established, the data from wholesomeness testing in vivo and in vitro studies are needed. Again, the extent of data will depend upon the nature of the novel food, its degree of similarity to established food products, and its expected role in the overall diet. Since traditional toxicological feeding studies will be rather unfitted to establish large safety margins for bulky foods, mechanistic approaches in the in vitro and in vivo tests are important as supplementary means together with human trials in establishing sufficient assurance regarding the wholesome use of the novel foods in the overall food supply.

The information needed for the assessment depends upon the nature and complexity of the novel food, its potential nutritional impact and the expected consumption level (never been eaten before, normal level, higher level). Especially the assessment needs to take into account the nutritional implications for population subgroups such as children, pregnant and lactating women, the elderly, groups with inborn errors of metabolism and other inborn diseases. Broad information on bioavailability of nutrients (protein, lipids, carbohydrates, vitamins and minerals) and changes in comparison to the food or food ingredient normally used should be considered. Where nutritional imbalance or interactions with other nutrients (or xenobiotics, e.g., drugs) can be expected, studies must clarify the significance of these. If appropriate animal models cannot be found, and if ingested in large amounts by humans, sufficient information must be provided through human trials and preferably consisting of both metabolic, and short-term and long-term clinical tests, eventually involving specific target groups.

In the case of novel foods which are or which contain live microorganisms, details of their health impact should be given, including their ability to colonize the human gut, their effect on the human gut flora, including examination of their potential infectivity/pathogenicity/toxicity, potential gene transfer and stability, their fermentation pattern, e.g., short chain fatty acid production.

The toxicological information necessary to assess novel foods which not are substantial equivalent has to be determined on a case-by-case basis taking into consideration the unique features of the individual novel food. The design of toxicity studies for the testing of novel foods in experimental animals need to built upon initial animal studies for nutritional values and bioavailability, to enable the separation of adverse effects due to
nutritional imbalances from inherent toxicity. Since no large safety factor can be derived from traditional animal feeding studies by including a bulk food in the test diet, the core study, i.e., a 90-day study, has to be expanded to include early biological markers for parameters such as general cellular toxicity, carcinogenicity, genotoxicity and DNA repair, oxidative stress, neurotoxicity and immunotoxicity. Results from standard in vitro tests on genotoxicity, cytotoxicity and tissue toxicity may add to the resolving capabilities of the in vivo study with regard to assessing wholesomeness of the novel food in question. The outcome of such studies as well as the intended use level in the human diet will determine the further testing strategy: whether human studies are needed and can be performed right away, or further animal studies should be initiated including second species toxicity studies, reproduction studies and long-term toxicity/carcinogenicity studies to determine the degree of nutritional-toxicological interaction.

Novel foods from plants, animals and microorganisms, as well as novel processes raise concerns about their potential for introducing food allergy. Such concerns may be met by demonstration of presence/absence of known epitopes for allergenicity in the novel foods and by results from the testing of the novel food in a combination of in vitro/in vivo tests as well as by results from the human clinic. Such tests may include among others determination of molecular weight of specific protein products (10-70 kDa) and stability of these proteins to heat, pH and gastrointestinal proteases. No generally accepted strategy for assessing the allergenic potential of novel foods with absence of epitopes of known food allergens has been developed yet.

When the nonhuman studies have determined the nutritional-toxicological limitations of the novel food, acceptability for general human consumption needs to be confirmed in human trials, since no large safety factor is derived from the in vivo and in vitro studies. The trials in humans should identify unexpected adverse interferences with other dietary constituents or with different health conditions and may make use of some of the biomarkers from the in vitro and in vivo studies. The human test package needs finally to include long-term human studies (>2 months).

3. **Rationale and circumstances when changes would be required in the evaluation of the safety of a food ingredient.**

The rationale and circumstances, when changes would be required in the evaluation of safety of a food ingredient, is given above, where the logic sequence of the stepwise approach reflects the increasing complexity of the scientific data needed for the evaluation of wholesomeness of the novel food item.

In our view each novel food or novel food ingredient should move through this three step approach allowing for the benefit of doubt whether it is substantial equivalent to an existing traditional food item or it has to be evaluated as a completely new, nontraditional food item.

In a general sense most of the traditional food plants from all over the world bred by traditional methods or genetically altered by self cloning may be candidates, which fulfill the criteria for marketing from step one. Her a very important international consensus is needed for defining the type and degree of variance which could be tolerated within the meaning of the word "substantial" in the term "substantial equivalence". This consensus should not only apply to food plants, food animals, and food microbiais, but also to chemically defined food ingredients as well as novel food processes.

At the step 2 level the approach for wholesomeness assessment of new traits and predominant secondary changes is straightforward by the application of the food additive safety approach.

At step 3 our suggestion is that the initial approach should be the 90 day study as the core study expanded to include a number of biomarkers for potential long-term effects both in the in vivo part and in simultaneous in vitro studies. If this core study does not clarify the long-term health issues, this calls for the long-term animal study to be performed in order to establish the margin of safety to the potential life time intake in humans. Since this margin of safety will be within a magnitude of 5 to 20 times, extended human studies are
needed before release to the gross market. Human exposure studies should include studies, which exceed at least two months.

There is a crucial need for the creation of a common scientific basis within the Codex system concerning the type and amount of data to be requested for the wholesomeness assessment of the novel foods. Likewise agreement in the assessment of the benefits/disadvantages needs to be established in the international community, since the generally narrow margins of safety which can be obtained from nonhuman and human studies will create the need for more precise societal cost/benefit analyses. Also claims regarding the potential health promoting effect of certain food items will need to be addressed scientifically in the same way as negative health effects. In this regard it might be worthwhile to look into the kind of data which some countries are requiring for the so-called "functional foods."

We hope that this paper does contain some reflections of interest to your process towards consensus. We can assure that a similar movement is on its way in Europe in these days.
RESPONSE #10

John N. Hathcock, PH.D.
Director, Nutritional and Regulatory Science
Council for Responsible Nutrition
1300 19th Street, NW, Suite 310
Washington, DC 20036-1609

Thank you for the letter of November 3, 1995 concerning the general principles of safety evaluation for food ingredients. I understand that this information is being requested by LSRO in order to fulfill a contract with the Food and Drug Administration. I understand further that the scope of this request includes whole food, food additives and GRAS ingredients, but does not include nutrients or other dietary ingredients in dietary supplements.

You requested comment on strengths and weaknesses of the current approach, proposed changes, and rationale and circumstances when changes would be required. Also, you provided seven areas of issues and questions from FDA for consideration as background.

I will first discuss the seven issues identified by FDA and then use the rationale and examples within this discussion to develop the more general comments you requested.

FDA Issue #1: In what cases are animal feeding studies not necessary to ensure safety? As examples, do such studies need to be conducted for ingredients that also occur naturally in food at similar or higher concentrations? Is it reasonable and necessary to test food-like substances for toxicity and nutritional influences recognizing the potential for confounding results? If so, how?

First, it is the amount consumed per day, not the concentration in food, that is directly relevant to safety. As an extreme example, if capsaicin were added to bread at the same concentration that it occurs in cayenne peppers, it would be at least intolerable and perhaps toxic. Thus, the amount of a particular food in the diet must be considered, along with the concentration in that food. Of course it may be argued that toxicity can be excluded only if there have been adequate trials of sufficient duration, with an appropriate range of dosages, and with sufficient endpoints being measured. The trap in this approach is that criteria and standards can easily be set to such demanding levels that no substance (not one!) can pass the test. Absolute safety requires the proof of a negative, and the entire national budget could be spent without "definitively" proving the safety of anything.

Animal studies should not be required if the concentration in the food to which it would be added in the proposed use would not generate intakes any higher that those resulting from consumption of normal amounts of foods with the substance as a naturally occurring component.

The issue of nutritional influence vs toxicity is complex. It must be recognized that there is no sharp boundary between anti-nutritional and toxic effects. Examples are given in the table below, with progression from non-nutritional effects at the top to purely nutritional effects at the bottom.

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxin carcinogenicity</td>
<td>Non-nutritional.</td>
</tr>
<tr>
<td>Lead toxicity</td>
<td>Mostly non-nutritional effects but also antagonizes absorption of some essential trace elements.</td>
</tr>
<tr>
<td>EFFECT</td>
<td>CHARACTERISTICS</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Copper-zinc antagonism</td>
<td>One mechanism for toxicity of each is antagonism of absorption and binding of the other.</td>
</tr>
<tr>
<td>Dicoumarol toxicity</td>
<td>Antagonism of vitamin K function with decreased production of vitamin K-dependent clotting factors is the primary toxic mechanism.</td>
</tr>
<tr>
<td>Phytic acid antagonism of mineral absorption</td>
<td>The only known &quot;toxicity&quot; is through decreased absorption of minerals.</td>
</tr>
<tr>
<td>Amino acid adverse effects</td>
<td>At least three types exist: 1. Direct toxicity of the specific amino acid. 2. Imbalance that is alleviated by supplementing the first-limiting dietary amino acid or decreasing one or more of those in excess proportion. 3. Antagonism based on similar structure or chemical properties, probably resulting in competitive inhibition of absorption or transport.</td>
</tr>
<tr>
<td>Vitamin D toxicity</td>
<td>Exaggerated vitamin D function is the predominant mechanism of chronic vitamin D toxicity.</td>
</tr>
<tr>
<td>Carbohydrate induced GI tract disturbances</td>
<td>Bloating, flatulence, or diarrhea may result from incomplete absorption of carbohydrate due to excessive intake or incomplete digestion. Also, excess carbohydrates can displace other nutrients from the diet, resulting in a lower nutrient to energy ratio.</td>
</tr>
<tr>
<td>Inert fiber dilution of diet</td>
<td>Even if a fiber is totally inert, excess amounts can render the diet so bulky that adequate energy and nutrients cannot be consumed.</td>
</tr>
</tbody>
</table>

As illustrated by these examples, the distinction between "toxic" and "nutritional" mechanisms of adverse effects would require careful definitions and criteria. Such distinctions need to be made, however, because otherwise even normal dietary and usually non-adverse impacts, such as the decrease in zinc bioavailability after ingestion of whole-wheat bread, would be defined as toxicity.

**FDA Issue #2**: To what extent can chemical and structural similarity to food ingredients known to be safe obviate the need for animal or human testing?

Natural occurrence in foods at significant concentrations, together with structural or chemical analogies to a well-tested and safe substance should be adequate to support safety. For example, the common food carotenoids (e.g., lycopene, lutein, zeaxanthin) should be presumed safe at moderate levels because of their natural occurrence in foods and their similarities to beta-carotene. This conclusion would be further supported if all currently available animal data were consistent with the safety conclusion.

**FDA Issue #3**: What criteria should be used to determine when a treatment-related effect (including effects from nutritional imbalance or interference) is an adverse effect?

Effects with anti-nutritional mechanisms should not be judged adverse unless they are outside the normal, accepted range of impacts that occur from consumption of conventional foods. For example, antagonism of iron uptake by a food additive, consumed at the intended level of use, would not be considered unacceptable.
unless the effect is distinctly more pronounced than the effect of tea consumed within the usual range of intakes.

Regardless of whether the adverse effect is on a nutritional process or action, two characteristics have overwhelming influence on whether it is considered adverse: (1) permanence or transience of the effect, and (2) innate adverseness of the effect. For example, macular degeneration is qualitatively more adverse that conjunctivitis, either of which may vary in severity. In contrast, hepatitis varies over a wide range of quantitative severity, with the milder forms being fully reversible whereas more severe changes are not.

**FDA Issue #4:** Are there criteria that can be used to determine whether an adverse effect observed in a study is relevant to human safety, as opposed to an effect that is dependent on study design and has no relevance to safety under actual use conditions?

All in vitro effects should have very limited interpretation unless they are confirmed with in vivo methods. Animal studies may or may not be appropriate for extrapolation to humans, depending on many specific biological factors and the toxicity mechanism of concern. Adverse effects after parenteral or even gavage administration must be confirmed through dietary administration, in order to avoid confounding by a number of factors such as absorption rate differences, first-pass metabolism, and vehicle aspiration. The strength of evidence from dietary studies depends on the usual factors: number and type of studies, species, age, sex, levels and intervals of dosage, duration, and of course the number and type of endpoints measured.

**FDA Issue #5:** Under what circumstances should clinical studies in humans supplement, or replace, studies in laboratory animals? How will use of human data affect the need for safety factors? Which parameters should be measured and what study duration is necessary?

Human studies would be useful if not essential for safety evaluation of new chemical entities that are not sufficiently similar to substances found in relevant amounts in the food supply. Of course, clinical studies should be based on adequate information to allow safe and effective study design.

The availability of human data may, in general, allow for use of smaller safety factors. In some instances, such as with bimodal distributions of sensitivities, safety factors may not apply to all subpopulations. The susceptibility to dietary phenylalanine in normal, heterozygous, and homozygous persons for phenylketonuria provides an example of at least bimodal, if not trimodal, distribution. It is difficult to envision a safety factor that would appropriately cover this range without being inappropriately restrictive for some.

There is no end to the list of possible data requirements, for all possible variable in experimental design, prominently including test species, number and type of endpoints, dosage levels, and duration of treatment. Inappropriate expansion of the data demands, however, could define all substances as "unsafe." The only workable answers, therefore, are for endpoint selection commensurate with the state of science and knowledge of the substance and its effects and pattern of use, and for duration to be reasonable in relation to both intended use and the chronology of the biological effects suspected.

Also, epidemiological or anecdotal reports of associations of an ingredient with adverse effects must have sufficient strength to give credibility to both a cause-and-effect relationship and a dose-response relationship. The same demands for strength of evidence that are applied to health claims or nutritional support claims should be applied to claims for causality of adverse effects.

**FDA Issue #6:** Is there an agreed upon basis for determining the maximum level of an additive in a test diet, above which a study should be presumed unacceptable?

Is there an agreed upon basis? -- No. Should there be an agreed upon basis? -- Yes. A study should be deemed inapplicable if it meets any one of an appropriate list of criteria, such as if:
1. The dietary level is sufficient to cause adverse effects through dilution and the effects do not exceed those predicted, based on the degree of dilution.

2. The dietary level causes chemical or physical actions of a type that are impossible at lower levels, e.g., precipitation of crystals in the urinary bladder, corrosion of the GI tract mucosa, metabolic acidosis or alkalosis from dietary loading of acid- or base-forming elements.

3. The statistical power is insufficient to identify meaningful biological changes, especially in nonparametric endpoints.

**FDA Issue #7:** Can post-market surveillance (both monitoring of use and monitoring of adverse reaction reports by consumers and physicians) be used to ensure safety? For example, can it be used without compromising safety to verify exposure estimates or to eliminate the need for specific data prior to marketing, thus reducing the need to use worst case assumptions in a safety evaluation? If so, how could this be accomplished?

Post-market surveillance cannot be used alone to ensure safety. If animal and/or short-term human data suggest no harm, post-market surveillance may be used to make up for any suspected inadequacy in the length of clinical trials. Similarly, post-market surveillance may be used to look for effects in especially susceptible subpopulations for which adequate numbers of subjects are unlikely to be available for testing. Also, post-market surveillance should be sufficient to determine whether a food ingredient is safe at extreme levels of human intake, e.g., for the 99.99 percentile consumption level.

**GENERAL COMMENTS:**

1. **Strengths and weaknesses of the current scientific aspects of food safety evaluation.**

   **Strengths** include: Emphasis on a single chemical entity in order to "get at" whether the specific substance is safe; animal testing that involves oral dosing, several dosage levels, different durations of administration, and multiple endpoint screening; consideration of both animal and human studies when available; use of safety factors; and acknowledgment that absolute safety can never be demonstrated.

   **Weaknesses** include: Emphasis on a single chemical entity, with the implied assumption that combination with other material makes no difference (neither potentiation nor antagonism); nearly exclusive dependence on a toxicological testing paradigm that evolved around testing of micro contaminants (e.g., aflatoxin, cadmium, and organochlorine pesticides); lack of standardization of diets for test animals; reluctance to accept tests of ingredients that are mixtures; relative inflexibility in setting safety factors; and absence of a systematic method for giving appropriate proportional weights to different types of studies (i.e., in vitro tests, animal studies, epidemiological studies, and clinical trials).

2. **Proposed changes in the criteria for safety evaluation.**

   - Increase the emphasis that results of in vitro tests are, at most, only suggestive.
   - Require that animal studies include dietary administration of the dietary ingredient.
   - Increase the use of, and dependence on when appropriate, history of use as a component of conventional food. For example, the substantial natural occurrence of vitamin A2 in many sources of vitamin A suggests that this form has virtually a safety profile that is indistinguishable from that of vitamin A.
   - Improve the safety evaluation of macro ingredients, including a quantitative method for deciding which effects are "toxic" and which are simply the effects of dietary dilution or nutrient displacement.

Develop a systematic method of adjusting the size of safety factors that considers the test dose limitations for macro ingredients and the minimum acceptable intakes for essential nutrients.
3. *Rationale and circumstances when changes would be required in the evaluation of the safety of a food ingredient.*

- Require that animal studies include *dietary* administration (in contrast to gavage) because of the interaction of the test substance (proposed dietary ingredient) and other dietary components. This change could either enhance or decrease the toxic potency of any particular substance, but the test will be much more analogous to the proposed conditions of use as a dietary ingredient.

- Require consideration of the history of use related to natural occurrence in conventional foods.

- Expand the history of use principle to include consideration of the history of use of similar substances and comparative toxicology of the ingredient under consideration, in relation to other compounds with a substantial history of use. Carotenoids may provide several examples.

- Exclude consideration of physical processes such as crystallization when such process depends on virtually impossible intakes.

- Exclude from consideration nutritional effects that are (1) dependent on dietary dilution unless such effect occurs at intended or likely levels of usage, and (2) no greater than those that occur with common, desirable dietary patterns, e.g., decreased zinc bioavailability comparable to that resulting from consumption of normal amounts of whole-wheat bread.

- Identify appropriate safety factors for nutrients through a process that does not use default assumptions that identify acceptable levels below the recommended levels of intake.

You are to be commended to effectively addressing the issue of safety of food ingredients. I would welcome the opportunity to interact further in this process.
RESPONSE #11

Owen Fennema, Ph.D.
Professor of Food Chemistry
Department of Food Science
University of Wisconsin-Madison
1605 Linden Drive
Madison, WI 53706-1565

I am responding to your letter of 3 Nov 1995 regarding criteria for FDA decisions on food safety. I will confine my remarks to only one of the FDA questions: What criteria should be used to determine when a treatment-related effect (including effects from nutritional imbalance or interference) is an adverse effect? This question is directly relevant to an issue of central importance, namely, how to judge, with reasonable certainty, that a substance is not harmful under the intended conditions of use. This leads to what I believe is a question the committee should deal with: "How severe must an adverse effect be before it is judged harmful?"

In seeking an answer to this question, one must first decide what kinds of effects are relevant when considering harm. Are quantifiable, adverse physiological effects the only types to be considered (as is apparently now done) or are psychological effects also to be considered? Surely if consumption of a substance causes a marked change in one's psychological condition this must be regarded as harmful. This matter needs to be considered with great care because psychological effects will be far more difficult to accurately quantify than physiological effects.

After the first issue has been resolved, then the question originally posed can be addressed, i.e., from a regulatory perspective, how severe must an adverse effect be before it is judged harmful? Here are a few suggested criteria that may be useful to consider:

An adverse effect will be judged harmful if one or more of the following conditions exist:

- An accurately quantifiable, adverse alteration in the physiological or psychological status of humans (or more than x% of humans?) that is prolonged (persists for several days or longer once consumption of the substance is discontinued) or permanent.

- An accurately quantifiable, adverse alteration in the physiological or psychological status of humans (or more than x% of humans?) that is temporary (disappears rapidly when consumption of the substances under question is discontinued) but debilitating. Debilitating is defined to mean a significantly impaired ability to perform normal job functions, or a significantly impaired ability to engage in typical activities away from the workplace.

- An accurately quantifiable, adverse alteration in the physiological or psychological status of humans (or more than x% of humans?) that is temporary and nondebilitating, but falls outside the mean status of humans ± two standard deviations.

These criteria may be incomplete and deserving of rewording, but statements of these kinds need to be developed. I hope this is helpful.
RESPONSE #12

Theron W. Downes, Ph.D.
Professor
The School of Packaging
Michigan State University
130 Packaging Building
East Lansing, MI 4882401223

Thank you for your letter of November 3, 1995 requesting my views on the criteria required to establish safety decisions about new food ingredients. I feel honored to be included among those scientists whose views are being solicited. When I completed my first review of your request my feelings would better be described as humility and confusion. These feelings arose because;

1. a very strong background in biochemistry, physiology, and toxicology is required for serious discussion of the issues you raise, and

2. one focus of your request is the newly emerging food additives (e.g. fat substitutes, biotechnology products) which may be present at significant concentration in the diet. My personal experience has been almost exclusively at the other end of the spectrum with indirect food additives such as the recently approved petition for use of hydrogenated butadiene/acrylonitrile copolymer.

I know that your organization can call upon a large number of experts (internally and externally) who are highly qualified to address these subjects. I choose to believe that the inclusion of individuals like me was a conscious choice to include a broad range of views in your deliberations and ultimate report. With that in mind I offer the following general comments regarding the strengths and weaknesses of the current scientific aspects of food safety evaluation.

STRENGTH: The high burden of proof required for approval of a new food additive petition has served us well. The 1958 action shifting the burden of proof to the petitioner has resulted in a demonstrably "safe" food supply.

WEAKNESS. The high burden of proof required for approval of a new food additive petition. It is not by accident that I have used identical words to describe both the major strength and the major weakness of our system. I have often had to confront the view held by my clients that petitioners and approvers (regulators) have an adversarial relationship. There is no qualitative difference between these groups, only a quantitative one. The quantitative difference that exists relates to the question of how safe is safe.

The law calls for "a reasonable certainty of no harm." It is not possible to "ensure safety" with absolute certainty. The quest for clear answers to any and all questions leads to inordinate delays, often without any resulting benefit in terms of better understanding of safety questions.

When questions are received during the comment period about unexplained effects, the following two questions should be answered before regulators decide how to respond.

1. Is the effect real? If the effect lies within the confidence limits of the experiment (observations) little effort should be expended attempting to separate the effect and understanding the cause, unless

2. the effect is toxicologically significant. For example, a (not statistically significant) difference of 1% in weight gain in a treatment vs a control group is not toxicologically significant and petitioner should not be required to do more testing to respond to a commenter's question regarding such a difference.
The question of toxicological significance is the fundamental question you are attempting to answer. In many cases good metabolic data will provide the information needed to assess toxicological significance. A test animal is not a little human being but we do share numerous metabolic similarities. During the late 70s, research into the metabolic fate of vinyl chloride monomer (in vitro and in vivo) demonstrated clearly that a threshold existed and confirmed a "reasonable certainty of no harm."
RESPONSE #13

Richard M. Clark
Senior Vice President, General Counsel and Secretary
Kellogg Company
One Kellogg Square, P.O. Box 3599
Battle Creek, MI 49016-3599

Kellogg Company ("Kellogg") welcomes the opportunity to respond to the request of the Life Sciences Research Office ("LSRO") of the Federation of American Societies for Experimental Biology ("FASEB") dated November 3, 1995 with respect to the Food and Drug Administration's ("FDA") criteria for evaluating the safety of food ingredients.

Kellogg is particularly well-positioned to address this topic, since it is participating in the process to have the FDA recognize psyllium seed husk ("psyllium") as a "generally recognized as safe" ("GRAS") for use in grain-based foods. Kellogg's original petition concerning this matter was filed on October 10, 1989. See 55 Fed. Reg. 4481 (Feb. 8, 1990). After submitting extensive supplements to that petition setting forth the scientific literature about the safety of psyllium--including a 1982 report by the Select Committee on GRAS Substances ("SCOGS")--Kellogg, at the suggestion of FDA, contracted with LSRO to have an independent panel of scientists review the safety of psyllium at the proposed levels of use. That panel issued a report making a safety determination in December of 1993, which was transmitted to the FDA in March of 1994. Since then, Kellogg's petition has languished before the agency.

This inaction is by no means an isolated development. The GRAS procedure is usually inordinately and frustratingly lengthy. It has been reported that, as of December 31, 1991, 58 GRAS affirmation petitions were pending; of these 4 were filed in 1991, 4 in 1990, 8 in 1989, 6 in 1988, 2 in 1987, 8 in 1986, 5 in 1985, 2 in 1984, 3 in 1983, 2 in 1981, 1 in 1980, 1 in 1979, 3 in 1978, 2 in 1976, 2 in 1975, 1 in 1974, and 3 in 1973. Food Chem. News, p.2 (Jan. 27, 1992). Likewise, at the same time, there were pending FDA GRAS proposals that cover 64 direct food uses and 19 indirect food uses; many of these date back to the early 1980s or the 1970s. Id at 1. The agency therefore needs to develop improved evaluative criteria and processes so that GRAS petitions can be decided in a more efficient and speedy manner.

Turning to the specific questions raised by FASEB, Kellogg offers the following comments.

1. Strengths and weaknesses of the current scientific aspects of food safety evaluation. Kellogg believes that there are several weaknesses or inconsistencies in the FDA's safety evaluation procedure, as reflected in its experience in connection with the GRAS petition for psyllium.

   a. Need for animal studies. During the course of meetings about the petition for psyllium, an issue was raised by agency representatives about the potential need for multi generational animal studies of the type sometimes required for food additive petitions and for studies of carcinogenicity and reproductive toxicity of the type set forth in the "Redbook." However, such studies should be unnecessary with respect to a food ingredient such as psyllium, which has had a long history of use by man, either in foods or in bulk laxative products. In short, the FDA should confirm that there is no absolute requirement for extensive chronic, reproduction, carcinogenic, or teratology studies. This recognition would be consistent with some of its prior GRAS determinations.

   For example, in the affirmation proceeding involving low erucic acid rapeseed oil, it was noted:

   "The agency recognizes that the petition does not contain chronic, reproduction, or teratology studies for LEAR oil. FDA believes that these

5 Although the agency has withdrawn proposals pending since the end of 1985, it decided on December 30, 1991 to retain most of its pending GRAS affirmation proposals. See Food Chem. News, pp. 26-27 (Jan. 6, 1992).
types of studies are not necessary to evaluate the safety of LEAR oil because
the composition of the oil, except for its erucic acid content, is similar to other
vegetable oils. In addition, there are human and extensive animal studies that
indicate that this oil's nutritional and toxicological profile is similar to that of
other vegetable oils." (50 Fed Reg. 3475, 3752 [Jan. 28, 1985].)

As another example, the FDA recognized the safety of agar-agar, a soluble fiber, quoting from the report of the Select Committee on GRAS substances as follows:

"Although no specific studies of the carcinogenicity or other long-term
investigations of agar-agar have been made, this material has a long history
of use as a gelling agent and bulk component of experimental animal diets.
Because 2 to 5 percent of this material has been used routinely in control diets
in numerous studies without reported significant effects, it is reasonable to
conclude that even at these high levels, agar-agar produces no significant

Similar results have been reported with respect to other soluble fibers. Thus, pectin was found to be GRAS even though SCOGS' examination of that substance discovered no relevant reports as to its acute toxicity or carcinogenic or mutagenic properties. 43 Fed. Reg. 38591, 38592-93 (Aug. 29, 1978), finalized, 48 Fed. Reg. 51148 (Nov. 7, 1983). SCOGS likewise deemed guar gum GRAS even though the only toxicity studies were two
six-month feeding analyses on rats and monkeys. 39 Fed. Reg. 34201, 34201 (Sept. 23, 1974). Gum arabic was likewise initially deemed GRAS at specific limited levels even though "[n]either oral LD_{50} values nor long term
gum arabic studies have been reported." 39 Fed. Reg. 34203, 34203 (Sept. 23, 1974). These limitations were subsequently expanded, even though no new safety data were reported. 53 Fed. Reg. 5765, 5766 (Feb. 26, 1988).

More recently, the agency has affirmed as GRAS a microparticulated protein product sold as a fat substitute under the trade name SIMPLESSE. 55 Fed. Reg. 6384 (Feb. 23, 1990). There is no indication in the Federal
Register notice memorializing this determination that long-term feeding studies were needed to analyze the toxic or carcinogenic effects of this substance.

These past examples of the agency's previous common-sense approach to the lack of need for extensive animal testing of substances long ingested by humans is consistent with the legislative history underlying the 1958 amendments to the Food, Drug & Cosmetic Act ("FD&C Act"). Indeed, in the floor debates on those amendments, the FDA conceded:

"Our Department believes that it is not necessary to good public health
protection to have chronic toxicity studies conducted of common food
chemicals, such as salt, sugar, vinegar, baking soda, and a great many other
materials that have been in common use for a long time. As a matter of fact,
these substances have been established as suitable food ingredients through
feeding to generations of human beings. Further, if the legislation required
such common chemicals to the subjected to chronic toxicity tests on animals,
there would not be enough laboratory facilities in the country to handle the
testing job within a period of several years." (104 Cong. Rec. Pt. 13 (H.R.) at
17420 (Aug. 13, 1958) (letter of FDA Deputy Commissioner John Harvey,
included in statement of Rep. Delaney).)

Or, as one Congressman stated in earlier hearings, "legislation requiring exhaustive laboratory analysis, pretesting and reporting of the old, recognized, safe additives would serve no useful purpose and would be unduly burdensome upon both industry and Government." Hearings on H R. 4475, House Commerce Committee, 84th
Cong., 2d Sess. 40 (1956) (statement of Rep. Miller). See also id. at 27-28 (statement of Rep. Delaney) ("where the chemical has been used over a long period of time it does not need to be tested").

The doubtful need for animal studies with respect to ingredients having a history of safe human use has also
been raised by FASEB itself. Thus, in its 1987 report on the physiological effects and health consequences of
dietary fiber, LSRO observed that, given the multifactorial nature of the results generated in animal studies on the protective and/or ameliorative effects of fiber on cancer—which are dependent upon factors such as the type of fiber, its chemical composition, and differing experimental protocols—"[t]he relevance of these animal models to human cancer needs to be determined." Despite noting a conflict among the animal studies on some sources of fiber and carcinogenesis, FASEB nonetheless went on to conclude that Americans can safely increase their dietary fiber intake of 20-35 grams per day. Similarly, SCOGS' 1977 evaluation of the GRAS process noted that "the 'true' relevance of animal data to man has been subject to considerable debate" and that "[t]he correlation between carcinogenic effects on rodents and those on man is not sufficiently consistent for confident extrapolation."

In short, past GRAS affirmation determinations by the FDA, the Congressional history of the FD&C Act, and FASEB's own prior statements all support the view that multi generational animal studies or long-term carcinogenicity/toxicity studies are not a prerequisite to a finding of safety, especially where long-term safe human use is shown. The FDA should issue a general statement of policy on the lack of need for such animal or carcinogenicity/toxicity studies in appropriate circumstances, thereby helping to avoid any inconsistent application of GRAS safety evaluation procedures.

b. Need for only published scientific studies. In the GRAS petition process for psyllium, FDA officials also raised concerns about the appropriateness of relying on unpublished scientific studies, such as unpublished data submitted in some other FDA proceeding or to SCOGS. This should not be a matter of concern. The GRAS regulation merely indicates that safety should "ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information." 21 C.F.R. §170.30. Indeed, the FDA has often relied on unpublished information in making GRAS affirmation determinations. See, e.g., 53 Fed. Reg. 44862, 44864 (Nov. 7, 1988) (solicitation of unpublished studies regarding safety of various sugars); 53 Fed. Reg. 11247, 11249 (Apr. 6, 1988) (FDA relied on unpublished reproductive toxicity study to find nisin was GRAS); 52 Fed. Reg. 10884, 10885 (Apr. 6, 1987) (potassium lactate deemed GRAS even though "no published studies" were submitted); 50 Fed. Reg. 3745, 3752, 3754 (Jan. 28, 1985) (reliance on unpublished draft report on safety of LEAR oil); 49 Fed. Reg. 13346, 13346-47 (Apr. 4, 1984) (reliance on unpublished studies on safety of certain tocopherols); 48 Fed. Reg. 239, 240 (Jan. 4, 1983) (mixed carbohydrase and protease enzyme product deemed GRAS based on "unpublished animal feeding studies"). Well-designed scientific support for an ingredient's safety ought to be the key factor, not the source of that support. The agency therefore needs to clarify its policy about the use of unpublished data in GRAS petitions, again in order to avoid problems of inconsistent enforcement.

c. Use of drug studies to establish food ingredient safety. Another issue raised by FDA representatives during the GRAS petition process for psyllium was whether studies involving psyllium's use as a bulk laxative could be relied on to establish its safety as a food ingredient. There should, however, be no doubt as to the permissibility of using such studies. The "scientific procedures" prong of the GRAS definition is not limited to use in food. Thus, studies on psyllium as an ingredient in both drugs and foods can support expert opinions that the substance is GRAS as a food ingredient. In United States v. Dan-Mar Enterprises, Inc., Food Drug & Cosm. L. Rep (CCH) ¶38,215 at 38,883 (N.D.Ga. 1978), appeal dismissed, No. 78-3666 (5th Cir., Jan. 22, 1979), it was stated:

"[f]rom a scientific standpoint, the safety of a substance is not affected by whether it is labeled as a food or as a drug if it is administered under the same conditions, at the same dosage, and for the same period of time."

See also United States v. Naremco, Inc., 553 F. 2d 1138, 1143 98TH cir. 1977) (Court was willing to consider data related to drug use to determine safety even under "common use in food" standard if data reflect conditions producing long-term ingestion and approximating use as a food additive"). The regulatory history of other substances also suggests that scientific studies demonstrating safe use as a drug can form the basis of general recognition of safety as a food ingredient. Cf., e.g., 45 Fed. Reg. 61,474, 61,474-75 (Sept. 16, 1980). Thus, based on these precedents, the use of a substance in drugs ought to be considered in analyzing its GRAS status as a food ingredient; indeed, in its 1982 report, SCOGS did just that with respect to psyllium. The FDA needs to clarify its policy on this issue as well.
2. Proposed changes in the criteria for food safety evaluation. The foregoing suggestions can all be viewed as changes in the criteria for food safety evaluation, to the extent they address inconsistencies in the agency's implementation of the evaluative process and the need for further clarifications of the agency's policies.

a. Risk-benefit analysis. Another important issue that needs to be addressed by the FDA is the weighing of the health benefits of the food ingredient at issue against the risks associated with its use. This factor was stated to be a criterion for GRAS status as far back as the agency's 1976 Federal Register notice:

"The Commissioner concludes that it is appropriate to recognize that the benefit contributed by a substance is inevitably a factor to be considered in determining whether a particular substance is 'safe' (or generally recognized as 'safe') for its intended use. The term 'safe' is to be given its ordinary meaning, and in its common usage the term is understood to carry an assessment of benefits and risks. It is true . . . that minor food additives are not approved at levels that may present a hazard to the normal consumer. This result is required by the act because the benefit or a minor food additive is too small to justify the imposition of a known risk to normal consumers: use of such ingredient at levels that may present a hazard to the normal consumer would not be 'safe'. However, this result does not necessarily follow in the case of important food additives. For example, if it were found that a major food source such as meat or grain was associated with the development of chronic diseases in normal individuals, it would not necessarily follow that the food was unsafe within the meaning of the act. The ordinary understanding of the term 'safe' would require some benefit-to-risk analysis in such circumstances.

Another example relates to the incidence of allergic reactions to particular food ingredients. Adverse reactions caused by allergy are clearly a consideration in determining whether a food ingredient is safe. Ordinarily, the incidence of allergic reactions from a food additive cannot be considered because data and test protocols do not exist. When data exist, however, they may be considered, and an assessment of benefits and risks becomes relevant. For example, if it were determined that both a particular emulsifier and a particular fruit resulted in the same unusually high incidence of allergic reactions, one might reasonably conclude that the emulsifier was not safe but that the fruit was safe. Such conclusions would simply represent common understanding of the concept of safety." (41 Fed. Reg. 53600, 53601 (Dec. 7, 1976).)

Despite this broad policy pronouncement, however, the FDA often fails to take adequate account of the health benefits of a food ingredient in analyzing its safety and in speedily making a GRAS determination. Kellogg believes that this has occurred with respect to its psyllium GRAS petition. The agency needs to develop criteria for implementing this risk-benefit analysis more fully.

b. Nature of scientific recognition of safety. In a 1985 Federal Register notice, the FDA has also recognized that "safety" is inherently a subjective evaluation and that different groups of scientific experts may disagree over whether a food ingredient is "safe":

"'Safety' is a conclusion based on evidence, but it is also a subjective and relative term. Although evidence used in a safety decision is concrete and includes such items as documentation of the use and of the experience of using the substance in food, the interpretation of the evidence reflects the training, experience, and cultural values of the person making the decision. These factors affect the decision about the importance or weight assigned to various reports on the substance, judgments about the probability and seriousness of
adverse effects resulting from exposure to the substance, and determinations about whether there are enough data to support a decision.

It is entirely possible for two groups of experts with similar training and experience in the evaluation of the safety of a food substance but who live in different cultures to disagree on a safety decision based upon experience through common use in food. Each group would be biased by the values held by its own culture." (50 Fed. Reg. 27294, 27295 [July 2, 1985].)

The agency, in considering the issue of the "general recognition" of safety, has said that it "requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances ... added to food." 21 C.F.R. §170.30(a). Likewise, in its 1976 notice, the FDA stated that a substance cannot be determined to be GRAS when its characteristics are known only to a few experts; instead, the substance must "be known throughout the community of experts qualified by scientific training and experience to evaluate the safety of substances added to food." 41 Fed. Reg. 53600 (Dec. 7, 1976). However, the agency has also recognized that there may be instances where information about an ingredient is not widespread so any consensus is difficult to obtain, but where a determination of general recognition of safety would nonetheless still be warranted:

"As a practical matter, general recognition among the community of experts in the United States that a substance is safe is not likely to be achieved unless information on that substance is distributed widely in the United States and thus is generally available to members of the community. The opinions of this diverse community would have to be obtained and examined to determine whether there is in fact consensus on the safety of the substance. Because information about the use of a substance may be generally available without being widely circulated in this country and because of the difficulties in demonstrating consensus, the appropriate alternative would be for the agency itself to judge whether a substance has been shown to be GRAS based upon its history of common use in food outside the United States. The experts at FDA are selected from the community of experts who are qualified to evaluate the safety of food ingredients, and, therefore, the opinions of FDA are representative of those held by the larger community. Moreover, FDA has been making determinations about the GRAS status of food ingredients since the passage of the Food Additives Amendment in 1958." (50 Fed. Reg. 27294, 27296 [July 2, 1985].)

Kellogg believes that the FDA should also consider—in situations where a consensus is not likely to be obtained or where different factions in the scientific community have differing views as to an ingredient's safety—the authoritative pronouncements of expert panels, such as the FASEB-sponsored panel that Kellogg used in the psyllium petition process. The agency has gone on record as challenging the appropriateness of relinquishing its responsibility to an independent panel of experts. 58 Fed. Reg. 2478, 2503 (Jan. 6, 1993). However, this view misstates the issue. Kellogg is not suggesting that the agency relinquish any responsibility; all it suggests is that a less rigorous review of the scientific evidence is needed where an independent body of experts (such as an FASEB-sponsored panel) has reviewed that evidence. This type of less rigorous review is especially warranted when the ingredient in question has beneficial aspects of which consumers should not be deprived. Kellogg also believes that the agency should articulate guidelines as to how it would treat safety issues when the scientific evidence is in discord. Where the food ingredient has known health benefits, Kellogg believes that such discord should not preclude a prompt GRAS determination.

3. **Rationale for changes in safety evaluation.** In addition to the foregoing, and in light of rapidly advancing scientific knowledge about the health benefits of certain food ingredients, as well as the expertise of food industry scientists most familiar with such ingredients, Kellogg believes that the FDA should give great weight to private GRAS determinations by a manufacturer.

The importance of the private GRAS determination in the context of the FDA's regulatory process cannot be understated. The agency has promulgated GRAS lists set fort at 21 C.F.R. Pts. 182 through 186. The lists
are not intended to be all-inclusive; as the FDA has acknowledged, "[i]t is impracticable to list all substances that are generally recognized as safe for their intended use." 21 C.F.R. §182.1(a). The omission of a substance from the GRAS list is therefore "not tantamount to a finding that the substance did not have GRAS status . . . ." 

California Canners & Growers Ass'n v. United States, 7 Cl.Ct. 69,112 (1984), rev'd on other grounds, 9Cl.Ct. 744 (1986). While agency reviews of the status of a substance is ongoing, the manufacturer of that substance or a product containing it is "free to assert that the substance was indeed GRAS within the scientific community." 7Cl.Ct. at 113. See R. Merrill & P. Hutt, Food and Drug Law 68 (1980) ("FDA has consistently . . . acknowledge[d] that a food manufacturer may determine for himself whether an ingredient that he desires to use can be considered GRAS").

The agency has repeatedly made statements recognizing this right of manufacturers to make private GRAS determinations. Thus, in 1985, it conceded that "persons normally are free to make their own determination about whether a substance is GRAS . . . ." 50 Fed. Reg. 27294, 27296 (July 2, 1985). That same year, Dr. Sanford A. Miller, then director of the Center for Food Safety and Applied Nutrition, and Richard J. Ronk, then deputy director of the same institution, told the Grocery Manufacturers of American that sugar beet fiber "would be considered GRAS and that manufacturers could make that determination themselves without a formal request to FDA." Food Chem. News, p. 20 (July, 1990). This point was reaffirmed by Hugh C. Cannon, the FDA's Associate Commissioner for Legislative Affairs, in a letter sent to Senators Boschwitz (R-Minn.) and Conrad (D-N.D.) on June 18, 1990: "[i]t was our intention . . . to convey that individual firms could, under the Act, make an independent determination that a particular food ingredient is GRAS and market the product based on such a determination." Id. at 19-20.

In light of this consistent history of regulatory recognition, Kellogg believes that the issue of the safety of a food ingredient can be resolved by having the manufacturer make a private GRAS determination if no prior agency recognition of safety exists. That determination should be sufficient, even if no formal request for a finding of safety is made to the FDA. In most instances, however, Kellogg expects that responsible manufacturers will seek to have the agency affirm the GRAS determination that has been privately made pursuant to 21 C.F.R. §170.35. While it is of course possible that the FDA may ultimately disagree with that determination, the effect of a manufacturer having made it should be to shift the burden of proof, "the agency would have to prove in court that the ingredient [at issue] was not GRAS." R. Merrill & P. Hutt, supra at 68. See Hearings on H.R. 3375, House Commerce Committee, 84th Cong. 2d Sess. 150 (1956) (statement of FDA Chief Counsel W. Goodrich) ("[w]e have the burden . . . of proving that a product is not generally recognized as safe in the courts"). Thus, until the FDA acts, a manufacturer's reasoned safety determination is entitled to a rebuttable presumption of validity. Moreover, until the agency has a justifiable basis for overturning any private GRAS determination, it should not issue public comments raising questions about the reliability of that determination. The food industry's safety determinations--especially those corroborated by an expert panel such as one fielded by FASEB--are entitled to as much respect as the agency's.

The FDA has said it will, in its discretion, accept without formal affirmation a manufacturer's safety determination, but has said that this discretion--at least in the context of food ingredients for which health claims are made--is most likely to be exercised for food ingredients in common use before January 1, 1958. 58 Fed. Reg. 2478, 2502-03 (Jan. 6, 1993). The FDA should make it clear that this discretion will be applied outside the health claim context as well, and should consider extending liberally the exercise of such discretion to food ingredients not commonly used before January 1, 1958, for which: (1) there is significant evidence of safe common use since that date, or (2) there is significant scientific evidence of safety that would justify a GRAS determination.

I hope these suggestions are useful to FASEB. If Kellogg can be of any further assistance to FASEB in its analysis, please do not hesitate to contact me.

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RESPONSE #14

F. M. Clydesdale, Ph.D.
Professor and Department Head
Department of Food Science
College of Food and Natural Resources
University of Massachusetts - Amherst
Chenoweth Laboratory
Amherst, MA 01003-1410

As I reviewed your letter and questions I came to several conclusions:

a) I haven’t enough background to answer all of these adequately.

b) If I had the background it would take me a month to do the topics justice.

c) Your committee can best handle this in its deliberations.

However, having said that I will try to present you with some brief thoughts in answer to your questions as they were presented.

1. If an ingredient is produced in a “new” way then animal feeding studies are necessary. I would think that in some cases where animal feeding studies weren’t essential than GRAS affirmation would apply.

   Yes it is necessary to do some type of toxicity testing. I will leave it up to the toxicologists to decide how.

2. It may obviate the need for longer term multi generational studies in several species. It would not obviate the need for all studies.

3. When effects are predictable and obvious as well as biologically plausible.

4. I think a list could be made to be used in judging this. Judgement is the answer. The Keystone report considered this area in some depth and should be referred to.

5. The answer to this will depend on the development of a matrix showing exactly what information is needed and derived from human studies versus animal studies. Evaluation of such a matrix will provide your answer.

6. No, but there could be for every group of related compounds.

7. Nothing can be used to “ensure” safety. Such studies can be used for monitoring to reduce risk of long term effects. The questions you ask would vary with the compound and with the effect. Again your committee would be helped by the development of a matrix.

I hope these thoughts are of some help.
RESPONSE #15

Myra Karstadt, Ph.D., Senior Scientist
Michael F. Jacobson, Ph.D., Executive Director
Center for Science in the Public Interest
1875 Connecticut Avenue, NW, Suite 300
Washington, DC 20009-5728

This letter and its attachments constitute the comments of the Center for Science in the Public Interest in regard to questions posed by the Food and Drug Administration (FDA) concerning testing of food additives. The questions were set out in FDA contract No. 223-92-2185, Task Order No. 9.

The seven questions posed to FASEB by FDA are, in general, so global that we cannot respond in detail. We would need much more specific information to reply to several of the questions. We have, therefore provided replies to several questions and indicated which questions we feel we cannot answer at this time. In addition, we have some general comments that may help FASEB in responding to the Task Order.

1. **Regulatory status of testing guidelines ("Red Book," etc)-** We are concerned that there is not mandatory quality assurance/quality control (QA/QC) process, with the force of law, for ensuring that studies are designed, executed, and analyzed/reported correctly. Tests must be carried out in a manner sufficient to enable FDA to determine whether a food additive meets the statutory standard for safety and the regulatory standard of "reasonable certainty of no harm." Our review of data for additives such as aspartame and aceulfame potassium, both of which have been approved for use by FDA, has only added to our firmly held conviction that there be mandatory criteria for assuring that high-quality tests will be carried out. Such criteria should be implemented through notice-and-comment rulemaking, and should result in a regulation in the Code of Federal Regulations.

   We are not asking for mandatory status for the FDA "Red Book." We believe FDA should work with each company that wishes to submit a food additive petition for a direct additive to identify the tests necessary to provide an assurance that a determination of safety by the agency will be valid. Flexibility in choice of toxicity end points for which testing is necessary, choice of species for testing, choice of test methodology, etc., is critical, since there are many different types of food additives, and, when it comes to testing, there is not necessarily only one way to test or only one set of acceptable tests. Even though we would not want to see a regulatory mandate as to choice of tests, there should be a baseline set of toxicity data required for all food additives. The "level of concern" approach in the Red Book is appealing in this regard.

   A model for agency-company interaction in design of testing programs for food additives could be the design of testing programs for chemicals under the Environmental Protection Agency's (EPA'S) program for implementing the Toxic Substances Control Act (TSCA). EPA staff work with companies to design test programs, which are then incorporated into what amount to consent orders, which have the force of law. The Toxic Substances Control Act specifically empowers EPA to require testing of new and existing chemicals. While the Food, Drug, and Cosmetic Act does not specifically mention a requirement for testing, we believe the statutory requirement that safety be assured before an additive is approved implicitly gives FDA authority to mandate testing, and this statutory authority should be called upon to set into regulations mandatory quality guides for testing of food additives.

2. **Testing in animals vs. testing in humans-** There are both advantages and disadvantages to testing in animals; a similar situation pertains to testing in humans. Design of a testing program for an additive many necessitate studies in both animals and humans. The positive features and limitations of animal and human studies must be identified in terms of the data needs for the specific additive for which approval is being sought.

   For instance, animal studies carried out in rodents offer the advantages of having a large number of experimental subjects of genetically similar and well-characterized constitution, which have lifetimes that are short relative to those of humans. The animals are typically housed and maintained in environments that minimize exposure to germs and adverse influences such as air and water pollution. Test animals are fed or otherwise exposed to a test agent under highly controlled conditions, with completely characterized diets and assurance that the proper amounts of test agent are being administered.

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Clearly, small laboratory animals are very different from the people who will eat the food additives if they are approved for use in the American diet. The vast genetic variability of the population is in and of itself a virtual guarantee that the nature and extent of reaction of humans to a test agent will vary greatly, both qualitatively and quantitatively, from the reaction seen in experimental animals.

There are toxicity end points, such as cancer, where our experience tells us that results of animal tests of chemicals are generally predictive for humans. However, there are situations where humans may have reactions to chemicals that are not readily identifiable in animal tests. For instance, sulfites, long thought to be safe, turned out to be life-threatening for certain highly sensitive humans. The sometimes fatal effects of sulfites were identified because they caused acute reactions in special populations. Similarly, we are concerned that animal studies may not be adequate to characterize long-term effects such as subtle neurological or neurobehavioral changes on special human populations.

Our experience with olestra has provided insights into the special problems of testing of macroingredients, such as fat substitutes. These additives, which are designed to constitute a proportion of the human diet far greater than those usually associated with additives such as colors, flavors, and high-intensity artificial sweeteners, present particularly difficult testing questions. The “safety” studies for olestra, which utilized both animals and humans, may serve as an interesting model for determining how to allocate testing between animals and humans, depending on toxicity endpoint and special sensitivity of certain human populations.

In any case, we are strongly opposed to substitution of animal studies by unvalidated test systems, such as some of the cell-free systems being proposed at present. As an organization, we are sensitive to issues of animal rights. We oppose unnecessary testing n animals, and we support humane and ethical procedures in animal tests. However, we remain convinced that animal testing remains central to characterization of chemicals’ safety, and careful animal testing should continue. We do encourage exploration of any and all test systems that could ultimately reduce dependence on animals, but such tests would have to achieve the reliability we now associate with animal tests to be acceptable to assure safety of additives that could be consumed by many millions of Americans. Inasmuch as toxicity to special subgroups of the human population might not be identifiable prior to marketing approval of an additive could be conditioned upon careful post-marketing active surveillance of consumers of the additive.

3. Testing of additives must combine assured QA/QC with flexibility of design and execution- In summary, we conclude that, considering the wide range of chemicals that may be used as additives, it is appropriate that FDA’s testing criteria provide appropriate flexibility as regards determination of which tests are needed to provide the data needed for determination of safety and how to carry out the tests. However, this flexibility as to which tests to carry out must be coupled with a regulatory requirement that assures high quality of the tests. Companies wishing to market food additives must work with FDA staff to develop testing programs that meet these standards.

Attachments
Question 2

Structure-activity relationships (SAR) might be useful in evaluating the types of tests to which food ingredients should be subjected, and in determining whether tests are needed at all. However, validation of applicability of use of SAR for such ingredients would be needed before such an approach could be applied in food safety determinations. Given the great variety in the nature and complexity of chemicals that make up the universe of food ingredients, extensive validation studies may be necessary. Experience from use of SAR for evaluation of toxicity of industrial chemicals may or may not be applicable. We favor caution in using SAR to exclude testing unless extensive validation of the methodology is available.

Question 4

There has been a good deal of controversy in recent years about the applicability of adverse effects, especially cancer, that are seen when animals are administered quantities of a chemical at dose levels far above those normally encountered by humans. So long as fairly small groups of animals are used for toxicity tests and each animal "stands in" for thousands or millions of people potentially exposed to the chemical, it will continue to be necessary to dose animals at high levels in order to elicit effect incidences sufficient for good statistics. Dosing animals at levels similar to those people experience will not elicit sufficient numbers of adverse effects unless treatment groups are correspondingly increased. Increasing the size of test groups by a factor of, say, 1000, in order to improve the chances of eliciting adverse effects at low doses is unrealistic.

Use of high dose levels in cancer tests have been criticized by those who claim that different toxic effects occur at the high levels than at lower ones, increasing the likelihood of occurrence of cancer at the high levels. We do not believe this is generally the case.

As regards the applicability to the human experience of positive results from tests in which chemicals were administered to animals using a route different from that of interest (diet or possibly gavage in the case of food additives), in general we would place greater value on data obtained by the immediately relevant route. However, information on movement of the chemical once it enters the body by whichever route, as well as data on target organ toxicity, are necessary before making a final decision as to whether and how to discount data from studies conducted using a route of administration other than that of interest.

It is also true that animals are often administered food ingredients on a continuous basis while people may ingest the ingredients only infrequently. As is the case for use of high doses, continuous administration increases the likelihood that an effect will be elicited and is therefore necessary given the small number of animals used in tests.
Those are three examples of test characteristics that may be considered unrepresentative of human exposure to food ingredients in “real world” conditions. However, all those characteristics of toxicology tests are necessary if animal tests are to be used, if only a limited number of animal tests are going to be carried out, and if the tests are going to be protective of the public at large. Criteria that can be used to determine whether an adverse effect is relevant to human safety are difficult to generalize without more specific information on the study parameters of particular interest to FDA.

Question 5

Olestra is a good example of a chemical for which clinical studies provided valuable information for evaluation of safety. For macroingredients like olestra, testing in humans both complements and supplements tests in animals. The standard scaling factors used to provide assurances of safety when toxicity tests are carried out in animals don’t work for macroingredients, where both animals and humans may consume the ingredient at percent levels in the diet, rather than in the parts per million or parts per billion often associated with food additives such as artificial colors and flavors.

Clinical studies can prove particularly useful when information is needed on how consumption patterns (as, when food is consumed, with what other foods) affect development of adverse effects.

Obviously, only certain effects—such as gastrointestinal disturbances or acute neurologic reactions—can be identified in human studies. Detection of cancer, birth defects, etc., would not be possible within the timeframe for review of food additive petitions.

All human testing is limited by ethical constraints: there are some things one simply cannot do to humans but can do to animals, such as removing organs for analysis. One of the reasons animal tests remain central to safety evaluations for food ingredients is precisely this need to carry out invasive procedures that cannot be done on humans.

As noted above, it is not possible for us to generalize as to which parameters should be measured and the appropriate duration of a study. That will vary from ingredient to ingredient.

Question 6

NTP generally limits chemicals tested in diets to 5% of the diet. Exactly what the top dose should be will vary with the nutritional effects of high-dose feeding of a chemical. Clearly, if a dose of a chemical being tested has significant adverse effects on nutrition, growth and basic physiological functions, that dose and levels above it are not acceptable.

Question 7
Post-marketing surveillance cannot be used to ensure safety. Voluntary reporting of symptoms to an 800 number does not give any assurance of obtaining data of a quality or volume sufficient for statistical analysis. This is especially the case if the 800 number is being run by the company whose ingredient is being evaluated. We have had experience with this sort of reporting scheme, since Procter & Gamble conducted a study of “real world” consumption of olestra snacks using both an 800 number during the study and an in-person questionnaire administered at the conclusion of the study. Procter & Gamble’s data demonstrate quite well that reports to the 800 number were few in number, and evaluation of the reports by company physicians, which likely reduced the number of reports of illness characterized by the company as “adverse experiences,” probably further diminished the utility of this reporting methodology. The inadequacy of the 800 number was confirmed by the results of the questionnaire, which was itself limited in utility because of design and recall problems, but from which a far higher incidence of illness among consumers of olestra snacks was reported than was obtained through the 800 number.

In addition to difficulties likely with obtaining sufficient numbers of reports of illness for statistical analysis, there would be all sorts of problems attendant on linking illness with poorly documented consumption. Also, post-marketing surveillance might not pick up sufficient information on particularly vulnerable population subgroups, whose consumption patterns could be estimated using scenarios while safety evaluation is in progress. Therefore, post-marketing data should not be used to replace “worst-case” consumption scenarios when safety of a food ingredient is being evaluated prior to marketing.
RESPONSE #16

Margaret Gilhooley
Professor of Law
School of Law
Seton Hall University
One Newark Center
Newark, NJ 07102-5210

In your May 17, 1996 letter, you renewed a request for comments on a project being conducted by FASEB for the Food and Drug Administration on "Alternative and Traditional Approaches to the Safety Evaluation of Food Ingredients."

The illustrative questions primarily concern matters of scientific expertise. I am a lawyer, and law professor, and while I have worked on food issues at FDA and teach a Food and Drug course, I cannot comment on the scientific merits. Your letter also indicates the project concerns new foods, but does not identify them. Without having some idea of the character of the new foods, it is difficult to comment upon the procedures for evaluating them, even from a general policy viewpoint. FDA has, of course, already issued a policy statement on the regulation of foods developed through biotechnology. Thus, I assume you are dealing with foods that are new in some additional way. It is also not clear whether the project concerns foods being considered for food additive approval or GRAS recognition.

One questions asked about the use of post-surveillance measures to ensure safety. I have not had an opportunity to do legal research on this matter, but will add a few comments from a policy perspective. Having complete studies before a food is approved is, of course, an idea approach. Nonetheless, there could be situations when it is not possible to obtain all the information in advance, and this seems the most persuasive reason for relying on post-marketing data. In the drug area, FDA has also provided for Phase IV post-market testing, although, in the case of drugs, these products provide health benefits that can enhance the reasons for speeding approval. Whether post-marketing data can replace worst-case analysis is something I cannot comment on at this point, and would need more perspective about from the scientists.

When post-marketing verification is warranted, the scientists should still be reasonably certain that the food is safe before use is approved, and there should be reliable means of post-marketing verification. There means could include independent surveys of consumers or medical monitoring or a segment of the population. The Olestra experience may provide a model. In addition, there should be expeditious procedures to change the use levels or revoke approval if the post-marketing surveillance reveals unexpected problems. The approval should be conditioned on implementing these changes without waiting for lengthy food additive revocation procedures.

I have not had time to consider these matters in any detail. I hope these comments will be of some assistance.
RESPONSE #17

Edward S. Josephson, Ph.D.
Adjunct Professor
University of Rhode Island
Food Science & Nutrition Research Center
420 Liberty Lane
West Kingston, RI 02892-1802

I had to overcome my reluctance to respond [to LSRO letter of May 17, 1996] because I am not a professional toxicologist although I have spent a good part of my career in close association with toxicologists and what I submit as input is probably well-known to FDA. My comments follow:

1. Chemiclearance of foods processed by exposure to ionizing radiation. Beginning n the 1950s, the method used to assess safety for consumption was based upon animal feeding studies over several generations with up to 35% of the calories derived from the particular irradiated food being assessed for safety for consumption. In attempting to cover all classes of foods, a typical commonly consumed food from each major class was subjected to these long term and very costly studies. It is estimated that the U.S. Army spent over $6 million between 1955 and 1965 assessing safety for consumption of 21 irradiated foods only to find that tests designed with the state of the art of the 1950s were not, according to FDA, suitable for assessing wholesomeness by the criteria of the late 1960s.

It was during my last years in the 1970s as head of the Army's food irradiation program that Drs. Irwin Taub and Charles Merritt devised the chemiclearance principle in assessing safety for consumption. The principle was based upon the finding that the radiolytic products (numbers, types, and quantities) depended upon the conditions of radiation (e.g., dose, dose rate, presence or exclusion of oxygen in the radiation milieu, temperature of the food during radiation). Foods of similar chemical composition (e.g., beef, chicken, pork) would yield similar radiolytic products. Therefore, a complete long-term conventional toxicology study on chicken showing safety for consumption and identification of its major radiolytic products should prove wholesomeness of a related food (e.g., beef) if the radiolytic products of beef were similar to those found in irradiated chicken. Based upon the classical toxicological study of irradiated chicken and similarity of radiolytic products, FDA is now evaluating safety for consumption of foods of porcine, ovine, equine, and bovine origin without requiring costly long term studies of individual members of the classes of meats listed.

2. Finding a marker in the food treated with chemical which could be used in the overall assessment of safety. This may be more easily said than done, but should be explored. It could involve the mode of action of the chemical, targeting enzyme systems and specific nutrients. It appears that a research program to study the mode of action of a chemical additive could lead to markers affected by a particular chemical which in turn could lead to a rapid, less expensive method to assess safety for consumption.

3. Between 1946 and 1952 I was involved at the National Institute of Health on chemotherapy of malaria. My colleagues and I tested representative drugs of the 8-aminoquinoline class which were shown in clinical trials to be effective in preventing relapses in humans infected with vivax malaria. By performing in vitro tests with this organism in a blood based medium developed by Geiman and McKee of Harvard Medical School, the drug was ineffective against the parasite. But when the drug was oxidized (either by in vivo metabolism or by just blowing air into the in vitro milieu), the oxidation product we isolated was extremely toxic to the parasite. We did not pursue this lead because of the de-emphasis in the late 1940s of research on infectious diseases in favor of emphasizing research on diseases of an aging population (cancer, heart, stroke, etc.).

In closing, I wish FASEB and its panelists success in endeavors to find better methods and models for assessing safety of chemical food additives.