Nutritional and Safety Assessments of Foods and Feeds Nutritionally Improved through Biotechnology: *An Executive Summary*

A TASK FORCE REPORT BY THE INTERNATIONAL LIFE SCIENCES INSTITUTE, WASHINGTON, D.C.

The global demand for food is increasing because of the growing world population. At the same time, availability of arable land is shrinking. Traditional plant breeding methods have made and will continue to make important contributions toward meeting the need for more food. In many areas of the world, however, the problem is food quality. There may be enough energy available from food, but the staple foods lack certain essential nutrients. In the developed world, demand for "functional foods" (that is, foods that provide health benefits beyond basic nutrition) is increasing. Nutritional improvements in foods could help to meet both of these demands for improved food quality. Modern agricultural biotechnology, which involves the application of cellular and molecular techniques to transfer DNA that encodes a desired trait to food and feed crops, is proving to be a powerful complement to traditional methods to meet global food requirements. An important aspect of biotechnology is that it provides access to a broad array of traits that can help meet this need for nutritionally improved cultivars. The new varieties developed through modern biotechnology have been identified by a number of terms, including genetically modified (GM or GMO), genetically engineered (GE or GEO), transgenic, biotech, recombinant, and plants with novel traits (PNTs). For the present discussion, the term "GM" will be used because of its simplicity and broad public recognition.

Foreword

Most of the initial crops derived from modern biotechnology (also known as genetically modified or GM crops) consist of varieties of maize, soybeans, potato, and cotton that have been modified through the introduction of one or more genes coding for insect or disease resistance, herbicide tolerance, or combinations of these traits. It is well recognized that absolute safety is not an achievable goal in any field of human endeavor, and this is particularly relevant with respect to ingestion of complex substances like food and feed. The safety of foods and feeds derived from such crops, therefore, was established using the internationally accepted concept of "substantial equivalence." A key element of this comparative safety assessment is that a food or feed derived from a GM crop is shown to be as safe as its conventionally bred counterpart. Application of the principle of substantial equivalence involves identifying the similarities and any differences between a product and its closest traditional counterpart and subjecting the differences to a rigorous safety assessment.

Today, GM crops include plants with "quality traits" that are intended to improve human or animal nutrition and health. These crops (for example, rice with provitamin A, maize and soybeans with altered amino acid or fatty acid contents) are typically improved by modifying the plant's metabolism and composition. In some cases, these modifications result in a product with complex qualitative and quantitative changes. Experts convened by the Food and Agriculture Organization (FAO), World Health Organization (WHO), and Organization for Economic Cooperation and Development (OECD) have agreed that the concept of substantial equivalence is a powerful tool for assessing the safety of food and feed derived from GM crops. This conclusion was based on the recognition that whole foods and feeds do not lend themselves to the standard safety assessment principles used for additives and other chemicals and that quantitative assessment of risk of individual whole foods from any source cannot be achieved (1996 Report of the Joint FAO/WHO Expert Consultation on biotechnology and food safety: review of existing safety assessment strategies and guidelines, Rome, Italy).

Substantial equivalence is not a conclusion drawn from a safety assessment. It is a process to identify differences that warrant safety assessments before commercialization. Therefore, an essential element in the application of the concept of substantial equivalence to nutritionally improved products is the availability of appropriate methods and technologies to identify biologically and/or toxicologically significant differences that require a safety assessment. Profiling methods (for example, metabolomics) that allow the simultaneous screening of many components without prior identification of each component can contribute to this purpose. Such methods have the potential to provide insight into metabolic pathways and interactions that may be influenced by both traditional breeding and modern biotechnology. A major challenge in the use of profiling techniques is to determine whether observed differences are distinguishable from natural variation associated with varietal, developmental, and/or environmental factors. Profiling techniques must, therefore, be validated and the baseline range of natural variations must be clearly established before they can be used in a regulatory framework. For now, these profiling methods may be useful primarily as prescreens for nutritionally improved products to aid in the identification of compounds that need to be evaluated.

In 2001, the ILSI International Food Biotechnology Committee convened a task force and an expert working group to develop a framework for the scientific underpinnings of the safety and nutritional assessment of nutritionally improved GM products. This working group consisted of individuals from leading scientific insti-

tutions with expertise in the areas of human and animal nutrition, food composition, agricultural biotechnology, food and animal feed safety assessment, and global regulations pertaining to novel foods and feeds. In addition, the document was reviewed by 23 experts worldwide, and an international workshop was convened to facilitate broader involvement of global stakeholders in developing and refining a safety and nutritional assessment framework for nutritionally improved products. Reviewers and workshop participants included food scientists; plant biotechnologists; scientists from regulatory agencies with responsibilities for food, feed, and environmental safety; human food and animal feed nutritionists; food toxicologists; representatives from the food, feed, livestock, and biotechnology industries; and public interest sector scientists.

The resulting document provides the scientific underpinnings and recommendations for assessing the safety and nutritional effects of crops with improved nutritional qualities. It includes terms and definitions for describing such products, identifies the key safety and nutritional challenges, and introduces potential approaches and methods to address those challenges. To keep this document to a manageable size, its scope was intentionally limited. The document does not discuss the safety or nutritional assessment processes for functional foods (that is, foods that offer potential health benefits that go beyond satisfying basic nutritional needs), food or feed traits that are principally targeting a health or pharmacologic benefit, or crops that combine (that is, stack) several improved nutrition traits into a single crop.

The document also discusses the extensive experience available from the commercialization of GM crops to date and focuses on the unique questions and challenges associated with nutritionally improved products. This is a forward looking document that attempts to incorporate the current scientific principles and acknowledges the concerns raised to date, but it has not been used as an opportunity to directly revisit specific arguments, nor does it address the scientific principles and rationale for assessing the environmental safety of improved nutrition crops.

Chapter 1 of this document presents a synopsis of modern agricultural biotechnology. Chapter 2 discusses examples of nutritionally improved crops under development and/or consideration. The safety assessment process for nutritionally improved foods and feeds is presented in Chapter 3. This assessment builds on principles and processes that have been successfully employed for GM crops with improved agronomic traits that are currently on the market. Chapter 4 focuses on the nutritional assessment process for nutritionally improved food crops, and Chapter 5 focuses on nutritionally improved animal feeds. An overview of analytical methods both in place and in development to identify unanticipated or unintended changes in nutritionally improved crops is provided in Chapter 6. Lastly, an analysis of possible postmarket monitoring strategies for nutritionally improved GM crops is presented in Chapter 7.

It is our intention that this document will serve as a key reference for scientific and regulatory considerations on both general and technical issues.

Background

The first GM crops to be planted on a widespread basis consisted primarily of varieties with improved agronomic characteristics. These have been widely adopted and safely grown and used on a large scale in an increasing number of countries. A newly emerging class of GM crops is being developed with a focus on improved human or animal nutrition. A number of these crops have reached the field trial stage and/or are advancing through regulatory approval processes toward commercialization. These nutritionally improved crops have the potential to help offset nutrient deficiencies; improve the nutritional value of foods and feeds; promote well-being through elevated levels of beneficial compounds; lower levels of natural toxins, toxic metabolites, or allergens; improve processing; and/or enhance taste. To keep this document to a manageable size, its scope was intentionally limited. The document does not discuss the safety or nutritional assessment processes for functional foods (that is, foods that offer potential health benefits that go beyond satisfying basic nutritional needs), food or feed traits that are principally targeting a health or pharmacologic benefit, or crops that combine (that is, stack) several improved nutrition traits into a single crop.

As long ago as 1263, the English Parliament decreed that nothing could be added to staple foods that were "not wholesome for a man's body." Consequently, a well established history and process for assessing the safety of foods introduced into the marketplace exists that long precedes the introduction of GM crops. The assessment of crops with improved nutritional properties, regardless of how those crops are developed, can follow these same well-established principles and processes to assure that the intakes of essential nutrients in animal and/or human diets are not compromised. A key purpose of the assessment is to determine if adverse effects on health are likely to result from the intended compositional change. This kind of analysis has already been applied in several countries to crops with altered composition, and the principles of the evaluation are applicable to all novel foods. The scientific procedures for this kind of analysis require an integrated multidisciplinary approach, incorporating molecular biology, protein biochemistry, agronomy, plant breeding, food chemistry, nutritional sciences, immunology, and toxicology.

It is well recognized that absolute safety is not an achievable goal in any field of human endeavor, and this is particularly relevant with respect to ingestion of complex substances like foods and feeds. The safe use of a given food or feed has typically been established either through experience based on common use of the food or by experts who determine its safety based on established scientific procedures. Starting in the 1990s, the standard applied to novel, especially GM, food and feed crops has been that they should be as safe as an appropriate counterpart that has a history of safe use. This comparative assessment process (also referred to as the concept of substantial equivalence) is a method of identifying similarities and differences between the newly developed food or feed crop and a conventional counterpart that has a history of safe use. The analysis assesses: (1) the agronomic/morphological characteristics of the plant, (2) macro- and micronutrient composition and content of important antinutrients and toxicants, (3) molecular characteristics and expression and safety of any proteins new to the crop, and (4) the toxicological and nutritional characteristics of the novel product compared to its conventional counterpart in appropriate animal models. The similarities noted between the new and traditional crops are not subject to further assessment since this provides evidence that those aspects of the newly developed crop are as safe as crops with a history of safe consumption. The identified differences are subjected to further scientific procedures, as needed, to clarify whether any safety issues or concerns exist. By

following this process, the safety assessment strategies for GM crops have proved, over the past 10 years, to be scientifically robust, providing a level of safety assurance that is comparable to, or in some cases higher than, that available for conventional crops. Approximately 30000 field trials have been conducted with more than 50 GM crops in 45 countries. As an endorsement to the robust nature of the comparative safety assessment process, more than 300 million cumulative hectares of GM crops have been grown commercially over the past decade with no documented adverse effects to humans or animals.

Numerous independent evaluations of GM crop assessment strategies by scientific organizations (for example, WHO, FAO, OECD, EU Commission, French Medical Association, U.S. National Academy of Sciences, Society of Toxicology) have concluded that current safety assessment processes for today's GM crops are adequate to determine whether significant risks to human or animal health exist. Indeed, a number of these reports suggest that the use of more precise technology for GM crops may provide a higher level of safety assurance for these crops than for conventionally bred plants, which are usually untested. For example, the 2001 European Commission Report (EC-sponsored Research on Safety of Genetically Modified Organisms; Fifth Framework Program—External Advisory Groups, "GMO research in perspective," report of a workshop held by External Advisory Groups of the "Quality of Life and Management of Living Resources" Programme) summarized biosafety research of 400 scientific teams from all parts of Europe over 15 years. This study stated that research on GM plants and their products following usual risk assessment procedures has not shown any new risks to human health or the environment beyond the usual uncertainties of conventional plant breeding. Another example is a 2002 position paper by the Society of Toxicology, *The Safety of Genetically Modified Foods Produced through Biotechnology*, which corroborated this finding. It is, therefore, important to recognize that it is the food product itself, rather than the process through which it is made, that should be the focus of attention in assessing safety. This paper goes on to state that the Society of Toxicology supports the use of the substantial equivalence or comparative assessment concept as part of the safety assessment of foods derived from GM crops.

The Assessment Process

The methods presently used to assess the safety of foods and feeds from GM crops with improved agronomic traits are directly applicable to nutritionally improved crops. Molecular characterization studies that assess the sequence and stability of the introduced DNA and studies that assess the potential toxicity and allergenicity of any new proteins produced from the inserted DNA are as applicable to nutritionally improved crops as to other GM products. Compositional analyses that quantify expected and unexpected changes in more than 50 key components (for example, proximates, amino acids, fatty acids, vitamins, minerals, antinutrients) for agronomically improved GM crops are also appropriate for nutritionally improved GM crops. In 2001/2002, the OECD published lists of analytes for the compositional evaluation of specific crops, with the understanding that the need for analysis of specific compounds should be determined on a case-by-case basis. The compositional analyses provide information on the concentrations of macronutrients, micronutrients, antinutritive factors, and naturally occurring toxins. A database that contains detailed information on the composition of conventionally bred crops has been developed and made available by the International Life Science Institute (ILSI) at www.cropcomposition.org.

Any single safety assessment study has strengths and weaknesses, which leads to the conclusion that it is unlikely that any single study is sufficient to assess the safety of a food product whether developed through biotechnology or any other method. Therefore, consideration of the sum total of studies that comprise the safety and nutritional assessment of the crop is necessary to reach a conclusion that the food or feed products derived from a new GM crop are as safe as the food or feed derived from the conventionally bred counterpart. The strength of the risk assessment depends not only on the sensitivity of any single method, but also on the aggregate sensitivity and robustness of the evidence provided by all methods combined.

Analysis of Composition

The fundamental concepts used in food/feed assessments have been refined through extensive international dialogue and consensus building. The key concept is the need to determine whether changes other than the intended new trait have occurred in the new crop. It is recognized that statistically significant differences between the modified crop and its counterpart do not necessarily imply an outcome that might have an effect on human or animal health (that is, the differences may not be biologically meaningful), but may indicate the need for follow-up assessment on a case-by-case basis. Also, the occurrence of unintended effects is not restricted to modifications introduced via biotechnology; unintended effects also occur frequently during conventional breeding. Therefore, the impact of the insertion of DNA into the plant genome as well as the potential of the introduced trait to alter plant metabolism in an unexpected manner must be evaluated in the context of natural variation present in conventionally bred plants.

A detailed agronomic assessment is one important way to help identify unintended effects. The agronomic assessment evaluates unintended effects at the whole-plant level (that is, the morphological phenotype and agronomic performance data such as yield). Targeted analysis of composition focused on possible changes at the metabolic level (that is, the biochemical phenotype) is also an important tool to evaluate unintended effects. Where crops have been modified with the specific intent to change nutritional characteristics, the analysis should include examination of metabolites relevant to the modified anabolic and/or catabolic pathways and the impact of such modifications on the metabolites in related pathways. In the case of nutritional improvements that do not directly modify specific metabolic pathways, special attention to the mechanism of action of the desired trait should be considered. Examples of such traits are crops expressing a protein with an amino acid composition that results in higher levels of specific essential amino acids or crops with other desirable functional or organoleptic properties.

Since the types of nutritionally improved crops anticipated are diverse, the safety and nutritional assessment of each new product should be approached on a case-by-case basis, building on the comparative assessment principles and methods applicable to any new food or feed. A significant change in the dietary intake of a nutrient is defined here as a change that meaningfully affects health, growth, or development. In addition, the safety assessment of foods and feeds containing improved levels of nutrients will take into account the frequency and quantities in which the food or feed is consumed in by humans or animals, as well as the existing knowledge concerning the safety of the nutrient in question. Conventional crops vary widely in composition, as indicated in the 2001/2002 OECD consensus documents and in the ILSI crop composition database (www.cropcomposition.org). Determining the most appropriate conventional comparator for a nutritionally improved crop needs careful consideration. In some cases, it may be appropriate to use the closest genetically related or near isogenic

variety, considering simply the nutritional impact of the altered component when the modified crop is used as a direct replacement of the comparator. In other cases, where the nutrient composition is altered to an extent that no suitable comparator can be identified within the same crop, the comparator may be a specific food component derived from another food (for example, a specific fatty acid profile). In these circumstances, the assessment should focus on the safety of the changed levels of the nutrient in the context of the proposed use and intake of the food or feed as well as the safety of the altered crop. It should also be noted that in cases where one part of the plant is eaten by humans (for example, grain) and other parts are eaten by animals (for example, forage) compositional analysis of both will need to be examined separately (for example, seeds vs. seeds and forage vs. forage) and may lead to different results. Targeted compositional analyses using validated quantitative methods will continue to be the core method to assess whether unintended changes have occurred.

Nontargeted Methods

Nontargeted "profiling" methods may supplement targeted analytical methods in the future for the detection of unintended effects in GM crops. Examples of profiling methods include functional genomics, proteomics, and metabolomics for analysis of gene expression (for example, mRNA), proteins, and metabolites, respectively. These methods provide a broad view of complex metabolic networks without the need for specific prior knowledge of changes in individual plant constituents or pathways. These techniques have the potential to provide insight into metabolic pathways and interactions that may be influenced by both traditional breeding and modern biotechnology. A major challenge in the use of profiling methods for the detection of unintended effects is determining whether any observed differences are distinguishable from natural qualitative and quantitative variation due to varietal, developmental, soil, and/or environmental factors. In other words, it must be assessed whether the identified differences are biologically meaningful. Nontargeted profiling methods may thus provide additional opportunities to identify unintended effects, but they must be validated for the purpose, and the baseline range of natural variations must be clearly established and verified before they can be used in a regulatory framework. Profiling methods could, however, target specific metabolic pathways and identify expressed genes, proteins, or metabolites for which specific quantitative analytical methods could then be validated for the regulatory studies. These methods could also be used to assess whether there were changes in associated metabolic pathways. Hence, these methods may be useful during the developmental phase of a product because they can help to focus the safety assessment process by identifying the exact compounds that need to be measured in a specific nutritionally improved product.

The Role of Animal Studies

Feeding studies in laboratory animals and targeted livestock species may be useful to assess the nutritional impact of the intended changes (for example, the nutritional value of the introduced trait). Studies in laboratory animals may also serve a useful role in confirming observations from other components of the safety assessment, thereby providing added safety assurance.

The safety of the intended changes to a crop are normally tested using a tiered approach consisting of bioinformatic structure–activity relationship investigations for sequence homology with allergens and toxins, followed by in vitro determinations of the digestibility of newly expressed proteins and in vivo studies with appropriate animal species. The types of changes assessed in this manner include the newly expressed proteins, any new metabolites present in the improved nutritional quality of the crop, and substantially altered levels of metabolites preexisting in the crop. Because the type of modification to each new crop is unique, the specific scientific procedures for an assessment should be determined on a case-by-case basis. For this purpose, existing OECD toxicology test protocols may be applicable. In some cases, appropriately designed animal toxicity studies can provide an additional measure of safety assurance. In general, however, such studies in laboratory animals and targeted livestock species are unlikely to reveal unintended minor compositional changes that have gone undetected by targeted analysis because they lack adequate sensitivity.

Numerous animal feeding studies have been conducted with approved and commercialized GM crops with improved agronomic traits. All published animal feeding studies have shown that performance of animals fed ingredients from GM crops was comparable to that of animals fed the conventional counterpart. Thus, it has been concluded that routine feeding studies with multiple species generally add little to the nutritional and safety assessment of GM crops that have no intended compositional changes.

Although animal feeding studies with crops (for example, maize, soybeans, wheat) that are normal components of animal diets can be relevant and meaningful, animal testing of some food products (for example, vegetables, fruits) presents additional challenges because animals may not normally consume these products (for example, macadamia nuts can be eaten by humans with impunity, but cause transient paralysis when fed to dogs). In addition, some nutritionally improved crops create special challenges when choosing a comparator. Examples of these challenges include crops with increased nutrient content that enhances animal performance and crops from which an edible coproduct may remain after the desired nutritional ingredient has been extracted for other purposes. It is noteworthy that the most appropriate comparator may, in some cases, be a formulated diet that allows for comparison of the nutritionally improved crop to the conventional crop supplemented with a purified source of the enhanced nutrient (for example, amino acid or fatty acid).

Animal studies also may play a role in testing the nutritional value of the introduced trait in a nutritionally improved crop. Analyses of nutrient composition provide a solid foundation for assessing the nutritional value of foods and feeds; however, they do not provide information on nutrient availability. Therefore, depending on the specific nutritional modification being introduced, it may be important to assess nutrient bioavailability in relevant animal studies. The intended changes in each nutritionally improved crop will determine which animal studies are most appropriate. Attention is drawn to guidelines being developed by an ILSI Task Force for animal study designs appropriate for nutritionally improved crops developed through biotechnology.

Postmarket Monitoring

The premarket safety assessment of GM foods and feeds provides a scientific basis for ensuring the safety of the food and generally eliminates the need for postmarket monitoring. The premarket safety assessment principles applied to foods derived from GM crops are the same as those applied to other novel foods improved through other processes or methods. These scientific procedures and principles provide the basis for concluding that foods from GM crops are as safe as foods with a history of safe use and consumption. Postmarket monitoring has not been a routine requirement in supporting the safety or regulatory approval of food products, except in a few unique instances where there has been a need to confirm premarket dietary intake estimates to ensure safety and/or

nutritional impact. For example, in some cases regulators have used active postmarket monitoring for novel (albeit non-GM) foods where such issues were identified in the premarket assessment of food ingredients (for example, potential for digestive tract side effects of olestra or confirmation of consumer intake levels of aspartame and yellow fat spreads enriched with phytosterols).

Postmarket monitoring may be appropriate when there is a need to corroborate estimates of dietary intakes of a nutritionally improved food with expected beneficial effects on human health. Postmarket monitoring must be based on scientifically driven hypotheses relative to endpoints that potentially affect human safety or health. The investigation of adverse events or the potential for chronic health effects, the confirmation of premarket exposure estimates, or the identification of changes in dietary intake patterns represent examples where, in very specific instances, hypotheses may be appropriately tested through postmarket monitoring programs. In the absence of a valid hypothesis, postmarket monitoring for undefined hypothetical adverse effects from foods from a GM (or non-GM) crop is not feasible and adds nothing to the premarket testing results, while potentially undermining confidence in the overall safety assessment process.

The success of any postmarket monitoring strategy is dependent on the accurate estimation of exposure in targeted or affected population groups and the ability to measure a specific outcome of interest and associate it with exposure. There must be traceability from field to consumer and the ability to control confounding factors. Adequate data must be available, therefore, to assess the use, distribution, and destination of the product or commodity within the food supply. The safety and nutritional quality of nutritionally improved products can only be fully assessed in the context of their proposed uses and consequent human and animal exposure/intake. For example, exposure to enhanced levels of dietary components, such as fatty acids, in particular foods needs to be assessed in the context of total dietary exposure, which may be derived from multiple sources. Although this must be performed on a case-by-case basis, the analysis itself need not be complex. Methodologies for assessing human intake of nutrients and other dietary constituents range from per capita methods to methods that use available food consumption databases or direct consumer food consumption surveys. The analysis does not differ, in principle, from that applied to new food ingredients and food and feed additives. Another factor that may complicate the evaluation of nutritional exposure is the variability of the human diet and the global difference in diets and dietary consumption and, as a consequence, the resulting broad distribution of individual nutritional states. Unfortunately, reliable comprehensive dietary intake data are only available for a few countries.

Conclusions and Recommendations

The crops being developed with a focus on improved human or animal nutrition hold great promise in helping to address global food security. The existing comprehensive safety and nutritional assessment processes used to assess the safety of GM foods and feeds already introduced into the marketplace are fitting for nutritionally improved crops, although some additional studies may be needed to assess potential human health effects resulting from changed levels of the improved nutritional factor(s). The comparative assessment process provides a method of identifying similarities and differences between the new food or feed crop and a conventional counterpart with a history of safe exposure. The similarities noted through this process are not subject to further assessment since this provides evidence that those aspects of the new crop are as safe as crops with a history of safe consumption. The identified differences then become the focus of additional scientific studies and evaluation. The types of nutritionally improved products anticipated are diverse; therefore, the safety and nutritional assessment of each new product should be approached on a case-by-case basis. Many nutritionally improved crops have modified biosynthetic and/or catabolic pathways, and the impact of such modifications on metabolites in those and related pathways should be specifically and carefully examined. The use of profiling techniques to detect unintended effects is still limited by the difficulties in distinguishing possible product-specific changes from natural variation due to varietal, developmental, and/or environmental factors, and therefore, building databases containing information on natural variation is of high priority. These profiling methods may be useful as prescreens to help focus the safety assessment process by identifying the specific compounds that need to be measured in a particular nutritionally improved product. Depending on the nutritional modification being introduced, it may be important to assess nutrient bioavailability in relevant animal studies. Animal studies can play an important role in assessing the nutritional impact of the intended changes (for example, the nutritional value of the introduced trait) and in confirming observations from other components of the safety assessment, thereby providing added safety assurance. Any postmarket monitoring that is deemed necessary must be based on scientifically driven hypotheses relative to endpoints that potentially affect human and animal safety or health. In the absence of an identified risk, postmarket monitoring for undefined adverse effects for foods from nutritionally improved (or any other) crop is virtually impossible to carry out, is unnecessary, and is inconsistent with, and may undermine confidence in, the premarket safety assessment process.

Recommendation 1. All nutritionally improved foods and feeds should be evaluated for their potential impact on human and animal nutrition and health regardless of the technology used to develop these foods and feeds.

Recommendation 2. The safety assessment of a nutritionally improved food or feed should begin with a comparative assessment of the new food or feed with an appropriate comparator that has a history of safe use.

Recommendation 3. The safety and nutritional assessment of any new nutritionally improved crop varieties should include compositional analysis. In cases where the nutrient composition is altered to an extent that no suitable comparator can be identified, the assessment should focus on the safety of the changed levels of nutrients in the context of the proposed use and intake of the food or feed.

Recommendation 4. To evaluate the safety and nutritional impact of nutritionally improved foods and feeds, it is necessary to develop data on a case-by-case basis in the context of the proposed use of the product in the diet and consequent dietary exposure.

Recommendation 5. Current approaches of targeted compositional analysis are recommended for the detection of alterations in the composition of the nutritionally improved crop. New profiling techniques might be applied to characterize complex metabolic pathways and their interconnectivities. These profiling techniques can also be used in a targeted fashion to generate information on specific nutrients or other metabolites. However, before using profiling methods, baseline data need to be collected and the methods must be validated and harmonized globally.

Recommendation 6. Studies in laboratory animals may serve a useful role in confirming observations from other components of the safety assessment, thereby providing added safety assurance. However, studies in laboratory animals and targeted livestock are

unlikely to reveal unintended minor compositional changes that have gone undetected by targeted analysis because they lack adequate sensitivity.

Recommendation 7. Animal feeding studies should be conducted in target species to demonstrate the nutritional properties that might be expected from the use of the modified crop, crop component, or coproduct.

Recommendation 8. The premarket assessment will identify safety and nutritional issues before product launch. It is unlikely that any new product with scientifically valid adverse health concerns will be marketed. Postmarket monitoring of nutritionally improved food products may be useful to verify premarket exposure assessments or to identify changes in dietary intake patterns. Postmarket monitoring should only be conducted when a scientifically valid testable hypothesis exists, or to verify premarket exposure assessments.

About ILSI

The International Life Sciences Institute (ILSI) is a nonprofit, worldwide foundation established in 1978 to advance the understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. ILSI also works to provide the science base for global harmonization in these areas.

By bringing together scientists from academia, government, industry, and the public sector, ILSI seeks a balanced approach to solving problems of common concern for the well-being of the general public.

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This Report will appear in its entirety in Issue 2, Volume 3 of IFT's e-journal:
Comprehensive Reviews in Food Science and Food Safety
to be posted online in the second quarter of 2004

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