



Nutritional and Safety Assessments of Foods and Feeds Nutritionally Improved through Biotechnology: Case Studies

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

During the last 2 decades, the public and private sectors have made substantial international research progress toward improving the nutritional value of a wide range of food and feed crops. Nevertheless, significant numbers of people still suffer from the effects of undernutrition. In addition, the nutritional quality of feed is often a limiting factor in livestock production systems, particularly those in developing countries. As newly developed crops with nutritionally improved traits come closer to being available to producers and consumers, we must ensure that scientifically sound and efficient processes are used to assess the safety and nutritional quality of these crops. Such processes will facilitate deploying these crops to those world areas with large numbers of people who need them. This document describes 5 case studies of crops with improved nutritional value. These case

studies examine the principles and recommendations published by the Intl. Life Sciences Inst. (ILSI) in 2004 for the safety and nutritional assessment of foods and feeds derived from nutritionally improved crops (ILSI 2004). One overarching conclusion that spans all 5 case studies is that the comparative safety assessment process is a valid approach. Such a process has been endorsed by many publications and organizations, including the 2004 ILSI publication. The type and extent of data that are appropriate for a scientifically sound comparative safety assessment are presented on a case-by-case basis in a manner that takes into account scientific results published since the 2004 ILSI report. This report will appear in the January issue of *Comprehensive Reviews in Food Science and Food Safety*.

Background on the Importance of Nutritionally Improved Foods and Feeds

The United Nations (UN) charter declared that freedom from hunger is a fundamental human right. Diets that are deficient in essential nutrients can be a pervasive cause of hunger and undernutrition. The UN Millennium Project recognized that the number of undernourished people in the world had fallen from approximately 1.5 billion in the early 1970s to around 850 million by the 1990s, and targeted to reduce this number by half by 2015. However, it is sobering to note that even the achievement of this goal will leave the world with more than 400 million undernourished humans.

More than 200 million of the world's hungry are children, and at least 5 million of them die each year from undernutrition. Dietary deficiencies take a staggering toll on physical and mental development, which has implications for educational achievement, work performance, and, consequently, economic prospects. Inadequate nutrition also contributes to death from a wide variety of infectious diseases, many of which would not be fatal in well-nourished children.

Insufficient food intake results in many forms of macro- and micronutrient undernutrition. Micronutrient deficiencies are widespread in developing countries. The World Health Organization (WHO) has recognized that such nutrient deficiencies have a catastrophic effect on the health and quality of life of at least 2 billion people. Deficiencies in micronutrients such as iron, vitamin A, iodine, zinc, and folic acid affect large numbers of people, espe-

cially children, resulting in significant morbidity and mortality. In many situations, deficiencies in energy and multiple nutrients occur, and these are thought to exert synergistically negative effects. One example is protein-energy malnutrition (PEM), a macronutrient deficiency that is often associated with micronutrient deficiencies. For this reason, most nutritional scientists believe that the long-term solution to under- and malnutrition will be achieved only when all people have access to a balanced, varied, and plentiful diet that meets the known nutritional requirements.

There is no single solution to the complex problem of undernutrition and malnutrition. One approach, undertaken by plant scientists, has been to improve the macro- and micronutrient content of staple crops consumed in developing countries. In addition to using the natural variation present in crop germplasm, modern biotechnology tools are also being used to develop these more nutritious crops. Crops that have been nutritionally enhanced through either modern biotechnology or conventional plant breeding can be thought of as being biofortified. They have inherent fortification in which the level of a nutrient in the crop is enhanced above that normally present. The new varieties developed through modern biotechnology have been described with various terms, including genetically modified (GM or GMO), genetically engineered (GE or GEO), transgenic, biotech, bioengineered, recombinant, and plants with novel traits (PNT). For the present discussion, the term "GM" will be used because of its simplicity and broad recognition.

Research Developments since Publication of the ILSI Document “Safety and Nutritional Assessment of Nutritionally Improved Foods and Feeds”

In 2002, a task force of international scientific experts, convened by the ILSI Intl. Food Biotechnology Committee (IFBiC), addressed the topic of the safety and nutritional assessments of foods and feeds that are nutritionally improved through modern biotechnology. In 2004, the task force’s work culminated in the publication of a report (ILSI 2004) that included a series of recommendations for the nutritional and safety assessments of such foods and feeds. This document has gained global recognition from organizations such as the European Food Safety Agency and has been cited by Japan and Australia in 2005 in their comments to Codex Alimentarius. The substantial equivalence paradigm, called the comparative safety assessment process in the 2004 ILSI publication, is a basic principle in the document. This paradigm is one of the topics discussed within the present publication to demonstrate how it can be implemented in the safety assessment process of specific nutritionally improved crops. The comparative safety assessment process is the starting point, not the conclusion, of the analysis. Significant differences in composition are expected to be observed in the case of nutritionally enhanced crops. These differences are intended and should not be considered negative findings because altered composition was the objective of the development process. Instead, the nutritional and safety implications of any potentially significant differences must be assessed on a case-by-case basis.

Since the publication of the 2004 ILSI report, research has progressed on several topics central to the type of data needed to complete a scientifically sound comparative safety assessment of a nutritionally improved food or feed crop. Those topics are presented in the specific case studies in this publication. However, the purpose of reviewing these developments is to present new information that might impact the appropriate form or amount of data for a scientifically sound comparative safety assessment process while clearly reinforcing the underlying principle of the comparative assessment process that is consistent with the 2004 publication.

One topic that has benefited from new insights is the analysis of genetic changes in GM crops compared to the genetic changes that occurred historically during plant evolution, crop domestication, and the many forms of “conventional breeding.” It is relevant to the discussion of case studies of nutritionally improved crops because 1 crop was developed through conventional breeding practices, while the other 4 were developed using modern biotechnology. Conventional breeding also provides a baseline that is required for the comparative approach. Conventional crops (that is, crops produced as a consequence of traditional breeding, natural selection) might be casually described as “natural” or characterized as unchanged over time, while GM crops are typically described as products of human intervention. However, human intervention has been as critical to agronomically viable, nutritious, safe, and palatable food and feed crops developed through conventional crop domestication and breeding practices as it has been for GM crops. The goal of domestication is to produce crops with uniformity and desirable agronomic traits, and not necessarily to have plants with increased fitness. In fact, recent evidence on the nature of the changes that occur during conventional plant breeding challenges this perception. The nature of the genetic changes to a plant species brought about by domestication and breeding can be larger in scale and less well defined than the genetic changes to a species that arise from the application of modern biotechnology. For example,

it has been stated that “the occurrence of unintended effects is not unique to the application of recDNA techniques, but also occurs frequently in conventional breeding” (Kuiper and others 2001), and that “in fact, conventional breeding programs generally evaluate populations with much wider ranges of phenotypic variation than is observed in transgenic programs” (Bradford and others 2005). The plants used as major food crops today that were produced by conventional breeding have changed more quickly (for example, over the past few hundred years) than would have been possible through “natural” evolution without human intervention. Furthermore, the changes are commonly in the opposite direction of Darwinian “survival of the fittest.” Natural selection creates resilient biological systems with properties that adapt to a variety of environmental conditions and ensures continuation of the species. Unlike natural selection, conventional plant breeding and domestication of many crops often create gene combinations that would not survive without ongoing human intervention.

In addition, it has become clear that major domesticated crops have a wide genetic diversity that reflects the various global environments in which they are grown, and that such diversity is possible because breeding often takes advantage of the hypermutable, genetically fluid characteristics of plant genomes. Extensive variation in DNA content (both amount and makeup) is normal within a species, so that members of the same species may possess a slightly different complement of genes or display heterogeneity within specific genes. DNA rearrangements and mutations are common, natural phenomena and can result in the loss of some proteins, the modification of others, and the creation of novel proteins. Scientific experts sponsored by organizations such as the Food and Agriculture Organization of the United Nations (FAO), the European Commission (EC), and the U.S. Natl. Academy of Sciences (NAS) have frequently studied variations due to breeding and modern biotechnology application. In each case, they concluded that modern biotechnology is no more likely to produce unintended effects than conventional breeding is. Indeed, many expert reviews concluded that the more defined nature of the changes introduced into crops via modern biotechnology may actually be safer than changes produced by conventional plant breeding.

For example, it has been demonstrated that insertion of an entire high-flux pathway into GM *Arabidopsis* plants was achievable without pleiotropic side effects when assessed by combined analyses of the morphological phenotypes or through metabolic and transcript profiling (Kristensen and others 2005). Similarly, extensive analytical comparison of conventional wheat to GM wheat expressing a high molecular weight subunit of the HMW subunit of gluten proteins showed that the expression of the transgene in the GM lines was as that of the corresponding endogenous genes, the GM and control lines showed similar stability in agronomic performance and grain functional properties when grown at multiple sites and years, the gene expression profiles in developing grains of GM and control lines are much more similar to those of the parental lines than are the profiles of lines produced by conventional plant breeding, and the metabolite profiles of control and GM lines usually fell within the range of variation that is observed between genotypes of the species or samples of the same genotype grown under varying environmental conditions (Shewry and others 2007).

The data currently used for the safety assessment of GM crops have focused on the potential perceived risks associated with modern biotechnology. There are now worldwide data from more than 10 y of commercial use of GM crops and over 2 decades of

research experience, and no verified adverse consequences have been reported (James and Krattiger 1996). These results allayed the concerns of many and resulted in greater acceptance of GM foods. Indeed, some scientists have begun to question the painstaking premarket safety assessment of GM crops as practiced in some countries, and recommend that the extent and type of data that are part of a current safety assessment be updated to reflect this extensive safe experience with GM crops, coupled with new information about plant genome plasticity. They suggest that refinements to the process could include incorporating factors such as “familiarity” (for example, for commonly used proteins such as CP4 EP-SPS, Cry1Ab, and PAT) and the gene source (for example, when the gene is from the same crop species or is one with a history of safe use) into the overall safety assessment, influencing the extent to which event-specific data are needed.

Recent reports have demonstrated that GM crops are often more closely related to the isogenic parental strain used in their development than to other members of the same genus and species. For example, metabolomic studies of *Solanum tuberosum* have shown that conventional plant breeding produces both intended and unintended effects and that insertion of transgenes can occur with little apparent effect on composition, even when the GM variety produces significant quantities of a new metabolite (for example, inulin) (Catchpole and others 2005). Indeed, when the metabolites (DP2-3 fructans) that accumulate because of the presence of the introduced gene and its expressed product were removed from the analysis parameters, multivariate statistical analysis showed no significant variation in the metabolic phenotype, including harmful glycoalkaloids, between the GM crop and the progenitor lines, whereas conventionally bred cultivars showed clearly separated metabolic phenotypes. Similar results have been observed at the level of the proteome (for example, the set of proteins expressed by an organism's genome) for other plant species.

In the 2004 ILSI report, it was suggested that it is unwise to set a fixed numeric limit to the variation permitted for a metabolite as a trigger for further safety assessment. It was instead recommended that limits should depend on the specific metabolite, its role in safety and nutrition, and the dietary pattern of consumption in the target population, thus making an arbitrary limit across all composition analytes of little value. Nonetheless, there continues to be misunderstanding about the comparative safety assessment process. Substantial equivalence is not a conclusion to be reached, but rather the starting point for comparing a novel product to something with a history of safe use, in which the identified differences are subjected to additional assessment. Attempting to demonstrate the absence of any statistically significant differences between the new crop and its conventional counterpart will clearly be futile for crops whose compositions have been deliberately altered. For the major commodity crops (for example, maize, soy), the content of nutrients, antinutrients, and toxicants are well known and have a long history. This enabled the Organisation for Economic Co-operation and Development (OECD) to establish a well-defined list of constituents that should be assessed for several of these major crops, even if some of these constituents are not nutritionally or toxicologically important. Major crops are frequently, but not al-

ways, chosen as the target for nutritional enhancement, and these OECD composition guidelines are appropriate for improved nutrition varieties of these major crops. It is important to regard nutritional changes in the context of that food's consumption by various groups in the population and its contribution relative to specific nutrients—obviously few foods are good sources of all, or even many, nutrients. Similarly, targeted analysis of the well-understood antinutrients and natural toxicants in the major crops humans and animals consume will reveal whether unacceptable changes have occurred that would warrant safety concerns.

Several case studies in this document involve introduction of a protein not currently present in the crop. Therefore, it is important to note that another ILSI IFBIC task force is developing the scientific basis and recommendation for a framework for the safety assessment of proteins. The report from this Protein Safety Task Force, which is expected to be published in 2007, will describe the characteristics of proteins and how such characteristics should drive the safety assessment. It will include recommendations for a tiered, weight-of-evidence approach to the safety assessment of proteins.

Within the 2004 ILSI publication, comprehensive, untargeted compositional analysis techniques such as metabolomics, proteomics, and transcriptomics were suggested as potentially useful tools to screen for unintended changes in food and feed crops. Efforts continue in these areas to standardize the reporting structure of such “-omics” data and to recommend current best practices. These are important steps to harmonize workflows and to enable queries of the metabolomes, proteomes, or transcriptomes of novel foods against databases in order to find meaningful unintended and unexpected events. However, to date, public repositories on baseline metabolomes, proteomes, and transcriptomes of crops (such as is available for composition data at www.cropcomposition.org) are just becoming available, and it will require substantial time and financial commitment to establish and maintain databases that are standardized, validated, and monitored. It is recommended that data from analyses of samples from different environmental conditions be represented within crop profiling databases to enable baseline assessments to which profiles of metabolites and proteins in novel foods may be compared, if deemed necessary.

At the time of the 2004 ILSI publication, many studies were in progress to determine if DNA or protein from GM crops could be detected in products from animals fed these products. Two recent reports reviewed publications of studies conducted in a range of livestock species (Flachowsky and others 2005; Phipps and others 2006). Fragments of DNA from multicopy endogenous genes were found at trace levels in specific tissues in some of the studies in this review, although these fragments were typically very small, and certainly too small to encode a functional gene. No fragments of transgenic DNA that could retain any biological activity were detected in any animal-derived products. These reviews of published reports, plus other publications, demonstrate that to date there is still no scientific evidence to suggest that milk, meat, and eggs derived from animals consuming GM crops are anything other than as safe as those derived from animals fed conventional crops.

Application of Risk Analysis to Improved Nutrition Crops

In the Codex Alimentarius model, risk analysis is composed of 3 elements (that is, risk assessment, risk management, and

risk communication). During risk analysis, the risks are to be weighed against other issues, such as the benefits, with the aim to ensure the highest appropriate level of public health protection and to strive for risk management transparency and continuous

communication between assessors and managers during the process. Implementation should be examined and reviewed for its effectiveness in protecting public health. The case studies of nutritionally improved crops in this document focus on recommended scientific assessments of possible risks associated with the new nutritionally improved food or feed. However, science-based premarket assessments, as currently performed, typically do not balance the assessment of potential risks with the intended benefits that accrue from use. For nutritionally enhanced crops, it is particularly important to balance the intended nutritional benefits (for example, improved health, decreased incidence of disease, suffering, and/or death) against the outcome of the risk characterization. The perceived hazards often represent relatively small risks, whereas the potential nutritional benefits are relatively large. For example, it has been estimated that the development of iron- and zinc-dense varieties of rice and wheat for India and Bangladesh could prevent 44 million cases of anemia over 10 y (Bouis 2002).

Some scientists have begun to ask if the premarket safety assessment used in many countries is attempting to achieve a standard of absolute safety by continually adding data requirements as newer analytical methods come available (Bradford and others 2005a, 2005b). These scientists suggest that, from a scientific perspective, the cumulative experience over several decades of assessing GM crop safety should allow us to determine which tests need to be applied to new GM varieties to determine if they are as safe as their traditional counterparts with a history of safe consumption. This process is relatively simple for some crop species, while others may require more extensive analysis—yet today, we subject all crop species to the same assessment process, regardless of potential risk. The fundamental concept of the comparative risk assessment process is that it enables a reasonable certainty that a new GM variety of a crop is as safe as the conventional varieties currently being safely consumed by humans and animals.

Case Studies

This publication applies the recommended principles for safety and nutritional assessments of nutritionally enhanced crops set forth in the 2004 ILSI publication to 5 examples of nutritionally enhanced foods and feeds. The case studies are used to illustrate how the 2004 recommendations provide a strong and robust paradigm for safety assessment for “real world” examples of improved nutrition crops. These case studies are at different stages of development; therefore they have differing levels of available data. Nevertheless, the recommendations can be drawn equally from the 2004 ILSI publication. Four of the 5 case studies represent crops in which the nutritional improvement was achieved through application of modern biotechnology (that is, recombinant DNA techniques), and 1 case study reviews a crop improved through conventional breeding. One case study examines a crop primarily used for animal feed, while the other 4 are examples of crops modified to improve human nutrition.

Food

The 4 food case studies illustrate the variety of improved nutrition crops that are currently being developed to address the dietary insufficiency for particular nutrients in specific locales.

Nearly 70% of the world's population relies on cereal grains as a dietary staple (FAOSTAT 2004). Rice is recognized as the most important cereal for human nutrition, providing more than 30% of the energy intake of the population of Asia. Maize ranks third, after rice and wheat, as one of the world's 3 leading food crops. Although maize grain is primarily used for livestock feed in developed countries, maize is a dietary staple in Latin America and Africa. Other crops such as sweetpotato are also important secondary staple foods for large numbers of people in Eastern and Southern Africa, especially for subsistence farmers. Sweetpotato is also an important component of animal feed in China. Most crops, and hence the food derived from those crops, are deficient in one or more essential nutrients, and the diets of many in developing countries that rely on these crops lack dietary diversity. A lack of dietary diversity directly increases the risk of nutrient deficiencies.

The 1st case study of nutritionally improved food crops targets increasing maize's nutritional characteristics for human consump-

tion and livestock feeding systems by increasing the level and quality of key nutrients such as protein and oil; this has been a long-term goal of conventional plant breeding. This case study describes “Double-Embryo Maize,” a variety being developed through modern biotechnology in which the grain contains 2 embryos, resulting in maize grain with higher protein and oil contents.

The next two case studies describe and compare 2 different nutritional improvements of “Sweetpotato.” Sweetpotato tuberos roots vary in color (white-, yellow-, orange-, red-, or purple-fleshed), with orange-fleshed types being particularly rich in β -carotene. The 2nd case study involves conventional breeding and selection of orange-fleshed sweetpotato as a crop biofortified with β -carotene to control vitamin A deficiency (VAD). The 3rd case study is based on the recognition that both the protein content and quality of sweetpotato are relatively low, such that improved protein content and quality through biotechnology could benefit animal feed and high sweetpotato-consuming populations at risk for protein-energy malnutrition (PEM).

The 4th case study is “Golden Rice 2,” in which the concentration of the most important provitamin A carotenoid, β -carotene, was increased through modern biotechnology to address VAD. It is estimated that 70 g (1/3 cup) of Golden Rice 2 may provide two-thirds of the daily recommended intake of vitamin A for a preschool child, therefore holding great promise to reduce VAD in developing countries.

Feed

Many nutritional limitations to livestock production are present in both developed and developing countries. For nonruminant livestock production systems, maize grain is often the preferred energy source; however, it is low in the essential amino acid lysine. Consequently, diets based on maize must be supplemented with lysine, either from crystalline lysine or from high-protein ingredients (for example, soybean meal, fish meal). The last case study discusses “Lysine maize,” a crop in which the lysine content of maize has been increased through biotechnology, making it possible to simplify diet preparation by reducing or even eliminating the addition of crystalline lysine or high-protein supplements to some nonruminant diets.

Conclusions

The crops being developed to improve human or animal nutrition hold great promise in helping to address global nutrition needs. The present examination of 5 case studies (four of which are GM crops) has reinforced the conclusion that the existing comprehensive safety and nutritional assessment processes used to assess the safety of GM foods and feeds already introduced into the marketplace are appropriate to ensure the safety and nutritional value of nutritionally improved crops. Additional studies may be needed, on a case-by-case basis, to assess potential safety or nutritional consequences resulting from changed levels of the improved nutritional factor(s). For both conventional and GM crops, the precom-

mercial breeding and development process (for example, selecting a single commercial variety from large numbers of crosses between conventional lines or from hundreds to thousands of initial transformation events for GM crops) eliminates the vast majority of conventionally bred varieties and GM events that contain unintended changes, winnowing down to a single commercialized variety or GM event. In addition, the selected commercial product candidate typically undergoes detailed phenotypic, agronomic, morphological, and compositional analyses to further screen for unintended effects that would limit commercial acceptance or product safety.

Recommendations

The current comparative safety assessment process provides assurance of safety and nutritional quality by identifying similarities and differences between the new food or feed crop and a conventional counterpart with a history of safe use. The similarities noted through this process are not subject to further assessment. The identified differences then become the focus of additional scientific assessment. A number of recommendations resulting from the safety and nutritional assessment of the 5 case studies presented in this document are consistent across all case studies. These consistently noted recommendations are listed below and confirm that the principles set forth in this task force's 2004 ILSI publication are sound.

Recommendation 1

The safety assessment of a nutritionally improved food or feed begins with a comparative assessment of the new food or feed crop with an appropriate comparator crop that has a history of safe use (the definition history of safe use is explored in a recent publication of the ILSI Europe Novel Foods Task Force).

Recommendation 2

To evaluate the safety and nutritional impact of nutritionally improved food and feed crops, 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 3

The safety of any novel protein(s) introduced into a crop needs to be assessed. It is noted that another ILSI IFBiC publication recommends a tiered, weight-of-evidence approach for the safety assessment of transgenic proteins.

Recommendation 4

Compositional analysis of crops with known toxicants and anti-nutrient compounds should include analysis of those specific analytes. If warranted, an evaluation of the targeted metabolic pathway should also be conducted to identify specific metabolites for inclusion in the compositional analysis due to safety and/or nutritional considerations.

Recommendation 5

The appropriate phenotypic properties of the nutritionally improved crop need to be assessed when grown in representative production locations as part of the overall comparative safety assessment process. Further study is warranted if significant unintended and unexplainable differences between the improved crop and an appropriate comparator are identified.

Recommendation 6

Studies with laboratory animals can confirm observations from other components of the safety assessment, thereby providing a sense of added safety assurance, although they may lack the sensitivity to reveal unintended minor changes.

Recommendation 7

While feeding studies with target livestock species are not part of the safety assessment, they are important to demonstrate the expected nutritional benefit of nutritionally enhanced feed crops.

Recommendation 8

Premarket studies in humans might be appropriate on a case-by-case basis to assess the nutritional effectiveness of the improved nutrition crop in those cases where alteration by conventional breeding would trigger similar studies.

Recommendation 9

Premarket assessment regarding the impact of the introduction of an improved nutrition crop on the nutrient intake of consumers may often be appropriate (for example, when changes in agricultural practices or changes in consumer-led dietary intakes are anticipated).

Recommendation 10

The scientific assessment of the possible consequences of the adoption of improved nutrition crops should balance not only assessing the potential risks but also considering the opportunity for benefits to alleviate undernutrition for a potentially large number of people. In this regard, it may be useful to think of benefits as the removal of the risk of harm caused by nutritional deficiencies. This will provide the relevant data required for a meaningful risk-benefit analysis.

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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Table of Contents

Front Matter	i
Executive Summary	1
Chapter 1: Background and Introduction to Case Studies	18
Chapter 2: Recent Developments in the Safety and Nutritional Assessment of Nutritionally Improved Foods and Feeds	35
Chapter 3: Double Embryo, High-Protein, High-Oil Maize Produced Using a Cytokinin-Based Flower Rescue	70
Chapter 4: Nutritionally Improved Sweetpotato	90
Chapter 5. Golden Rice 2	130
Chapter 6. Maize with Increased Lysine (Lysine maize – LY038)	155
Appendices:	

continued on next page

1. Vitamin A Deficiency: A Global Risk	179
2. Biosynthesis of β -Carotene.....	184
3. Physiology of β -Carotene.....	189
4. Protein Energy Malnutrition.....	193
5. Dereglulation.....	199

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