

9. Perspectives on safety assessment of foods derived from the next generation of recombinant-DNA plants

Introduction

In recent years, the genetic alterations in new plant varieties under development have become more complex, with more genes involved and with an increasing tendency to alter existing metabolic pathways or even introduce new ones. These “second generation” recombinant-DNA plants have been deliberately modified to express novel traits to enhance nutrition and health (e.g. increased vitamin levels) or to improve livestock feed. Unlike the first generation of recombinant-DNA crops, which were not intended to have altered nutritional properties and whose single-gene traits were relatively straightforward to assess for safety, these second generation products may be intentionally designed not to be substantially equivalent to their conventional counterparts. This may introduce new challenges for those tasked with assessing the safety of foods and feedstuffs derived from these recombinant-DNA plants as there may be no conventional comparator against which the foods derived from the recombinant-DNA plants can be measured.

The next generation of recombinant-DNA plants is likely to be genetically more complex (and may blur the boundary between foods and therapeutics e.g. nutraceuticals, edible vaccines and biopharmaceuticals). This will make the application of the concept of substantial equivalence less appropriate, and the safety assessment of such products is likely to depend on additional approaches to assessment and parallel improvements in the understanding of the relationship between plant composition and health impacts. Ensuring that the safety assessment takes into account the dietary needs and consumption patterns of potentially affected (sub)populations will be vital.

It is anticipated that GM food products that have been modified to be significantly different from their conventional counterparts will receive different, if not greater, scrutiny than those GM foods that have been approved by regulatory authorities to date. New analytical methods for predicting and assessing these differences are being considered (reviewed by Kuiper and Kleter, 2003). The utility of these methods is constrained at present by the fact that insufficient data are available to indicate if statistically significant differences that may be identified using profiling methods such as DNA or RNA microarrays or proteomics are biologically relevant from a safety standpoint.

Internationally, few attempts have been made to examine how best to assess the safety of GM foods with enhanced nutritional or health benefits. The International Life Sciences Institute has published a document that provides the scientific underpinnings and recommendations for assessing the safety and nutritional effects of crops with improved nutritional qualities (the document does not address GM foods that offer potential health benefits). 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 (ILSI, 2004). A more recent initiative has been undertaken by the Codex *ad hoc* Intergovernmental Task Force on Foods Derived from Biotechnology. In 2005, the Task Force agreed to initiate new work to develop an annex to its 2003 Guideline (see Appendix 2). The annex will elaborate on the guidance provided in the 2003 Guideline.

General principles for the addition of essential nutrients to foods

The Codex Alimentarius Commission (CAC, 2007) provides the guidance for the maintenance or improvement of the overall nutritional quality of foods through the addition of essential nutrients for the purposes of fortification, restoration and nutritional equivalence. The General Principles also address the addition of essential nutrients to special purpose foods to ensure an adequate and appropriate nutrient content. The General Principles aim to prevent the indiscriminate addition of essential nutrients to foods, thereby decreasing the risk of health hazard due to nutrient excesses, deficits or imbalances. The Codex introduced these general principles in 1987 with subsequent amendments. Internationally, there is increased understanding of nutrient enhanced or health promoting foods. It is however a scientifically more involved field of research requiring a different treatment compared with providing a crop variety with increased resistance to a disease, insect pest or herbicide, even when biotechnological tools are utilized for the purpose.

The general principles review by CAC (2007) focused on:

1. new methods of achieving addition or enhancement of the levels of essential nutrients in foods, including biofortification;
2. the need for additional approaches to controlling the addition of essential nutrients to foods, including discretionary fortification;
3. the addition to foods of bioactive substances.

Biofortification

The Codex review (2007) defines biofortification as the indirect addition of essential nutrients or 'other substances' to foods for the purpose of nutritional enhancement or health enhancement. In addition to direct addition of the nutrient to foods at the time of processing, it is possible indirectly to add the nutrients at an earlier point of food production. Genetic transformation using recombinant-DNA technology is one such tool, using which the plant or animal is enabled to produce the additional nutrient e.g. an enhanced beta-carotene level in rice (see Box 9.1).

Box 9.1. Golden rice

An example of this new generation of recombinant-DNA plants is the development of "Golden Rice" in an international network involving the European Union, India, the Philippines, Vietnam and Bangladesh (<http://www.goldenrice.org>). Dietary micronutrient deficiencies, such as the lack of vitamin A, are a major source of morbidity (increased susceptibility to disease) and mortality worldwide. This deficiency affects particularly children, impairing their immune systems and normal development, causing disease and ultimately death. The best way to avoid micronutrient deficiencies is by way of a varied diet, rich in vegetables, fruits and animal products. According to the WHO, dietary vitamin A deficiency (VAD) causes some 250 000 to 500 000 children to go blind each year. For people who live below the poverty line in many parts of the world, the common foods consumed, such as rice, need to provide vitamin A. However, rice plants produce β -carotene (provitamin A) in green tissues only and not in the endosperm (the edible part of the seed). In Golden Rice, genes have been inserted into the rice genome by genetic engineering that

account for the production and accumulation of β -carotene in the grains. The intensity of the golden colour is an indicator of the concentration of β -carotene in the endosperm. After the concept was proved in 1999, new rice lines with higher β -carotene content have been generated and are undergoing field trials. The risk analysis and regulation processes are being followed by adhering to the national system and the Codex guidelines in each country. The goal is to be capable of providing the recommended daily allowance of vitamin A - in the form of β -carotene - in 100–200 g of rice, which corresponds to the daily rice consumption of children in rice-based societies, such as in India, Vietnam or Bangladesh. In other countries, *Golden Rice* could still be a valuable complement to children's diets, thus contributing to the reduction of clinical and subclinical VAD-related diseases. *Golden Rice* is a product that does not create new dependencies or displace traditional cuisine and has the potential to save a large number of people from VAD-related diseases.

Box 9.2. Key features of biosafety considerations for nutritionally enhanced foods

a) Estimation of potential exposure distribution patterns:

how to go about determining potential exposure distribution patterns in both target and non-target populations of a country and evaluate the safety of such exposure in vulnerable groups. Although techniques are available to simulate such patterns using modeling, it is felt that there is no substitute for controlled trials and investigations, first in animals, and then in consenting, informed humans. In this perspective, an important social issue needs to be taken care of, which is to label the foods derived from recombinant-DNA in the marketplace to provide a means of identifying the GM foods in epidemiological studies as part of post-release monitoring and risk management.

b) Bioavailability: bioavailability analysis should be incorporated into regulatory reviews of all recombinant-DNA plants developed for enhanced nutrition or health. Bioavailability studies using cell cultures have been recommended before feeding trials are taken up and employ radiolabelled compounds to trace the fate of the nutrient upon metabolism in a cell (Wood and Tamura, 2001).

c) Upper limits of safe intake: the need to determine

upper limits of safe intake for the nutrient or bioactive substance is essential to eliminate any risk associated with excessive intake of the food. Upper limits of foods containing enhanced nutrients have to be determined for each targeted nutrient as different nutrients can have different upper limits for their safe intake in human beings. Recombinant-DNA plants with modifications of nutrients need to be clearly identified and efforts taken to prevent their use without informed consent. Safe upper limits of ingestion need to be established using the pure form of the targeted nutrient followed by the edible form of the foodstuffs, first in animals then in human volunteers.

d) Stability testing of novel proteins introduced into the recombinant-DNA derived crop as a foodstuff needs to be undertaken because the novel products may create unexpected toxic by-products, especially when the primary plant product is processed into different forms and preparations. The behaviour of these proteins, if unknown from other sources of food, must be subjected to testing in processing as well as storage, in addition to the toxicity testing of the product.

Based on the models developed in Canada (Health Canada, 2005), by the European Commission (EC, 2006), and by Rasmussen *et al.* (2006), an attempt is being made to identify threshold limits for enhanced nutrients so that the risk of indiscriminate addition of essential nutrients is reduced and their effects on health can be evaluated. Similarly, there is a need for further research to identify nutrient-wise (case by case) the minimum levels of addition of nutrients to a biofortified food so that its desired consequence is realized beyond the discernible effect, to enable properly informed labelling of the product.

The Independent Science Panel, launched in 2003 in the United Kingdom³⁴, has discussed the issue of biosafety of nutritionally enhanced transgenic foods in response to the questionnaire developed by the Codex targeting recombinant-DNA derived foods aimed at nutritional or health benefits. Some key features of the biosafety considerations for nutritionally enhanced foods and crops are described in Box 9.2.

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