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Review

GMO risk assessment around the world: Some examples

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All over the world, authorities responsible for the assessment and surveillance of foods and feeds derived using gene technology and the environmental impacts of genetically modified organisms (GMO) have chosen specific strategies to assess their safety. Although different regulatory frameworks are in place, almost all adopted risk assessment strategies are based on a common set of principles and guidelines. Here we provide some examples of these strategies and we compare them to highlight areas where an international consensus exists. Our hope is that even if limited, this short review can represent a first step towards the recognition of an international consensus and a broader dialog on GMOs regulation worldwide.

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Introduction

Risk assessment strategies applied in different countries across the world for the assessment and surveillance of foods and feeds derived from organisms modified using modern biotechnology are based on a common set of principles, built on the accumulation of experience and scientific knowledge over the past decades. These principles were first put forward in 1993 (OECD, 1993), and were further detailed by the *Ad Hoc* Intergovernmental Task Force on Foods Derived from Biotechnology of the Codex Alimentarius Commission (Codex Alimentarius, 2003), an international body jointly established by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) of the United Nations.

During the Scientific Forum organized by the European Food Safety Authority (EFSA) for its fifth anniversary (EFSA, 2007) as a unique occasion to discuss progresses and needs of various issues related to food safety, experts from various part of the world have discussed the experience gained so far in genetically modified organisms (GMO) risk assessment have tried to identify differences and similarities of the risk assessment strategies adopted in some countries, namely Canada, the USA, Australia/New Zealand and the European Union. The focus was primarily on food and feed safety assessment, although attention was also given to some environmental aspects. In the following sections, we try to schematically describe the discussion and the outcome of the Scientific Forum, with the hope to provide a first framework for further understanding of GMO risk assessment around the world.

Foods derived from biotechnology risk assessment

Codex Alimentarius Commission

Codex was created in 1963 by the Food and Agriculture Organization (FAO) and World Health Organization (WHO) to develop food standards, guidelines and related texts such as codes of practice under the Joint FAO/WHO Food Standards Program (www.codexalimentarius.net).

The main purposes of this program are to protect the health of consumers, ensure fair trade practices in food trade, and promote coordination of all food standards work undertaken by international governmental and non-governmental organizations. In 1999, Codex established the *Ad Hoc* Intergovernmental Task Force on Foods Derived from Biotechnology to develop standards, guidelines or recommendations, as appropriate, for foods derived with

the use of modern biotechnology. The Task Force developed three documents that were adopted by Codex in 2003: Principles for the Risk Analysis of Foods Derived from Modern Biotechnology (Principles Document), Guideline for Safety Assessment of Foods Derived from recombinant-DNA Plants (Plant Guideline) and Guideline for Safety Assessment of Foods Derived from recombinant-DNA Microbes (Codex Alimentarius, 2003).

The Principles Document was developed to provide a framework for performing risk analysis on whole foods derived with the use of biotechnology or on components of such foods. While Codex and member countries had had considerable experience performing risk analyses of chemicals intentionally added to or inadvertently present in food (such as food additives, pesticide residues and contaminants), there was, until recently, little experience evaluating the safety of foods themselves.

The Principles Document discusses risk assessment, risk management and risk communication, and describes the safety assessment as a component of the risk assessment. The essence of the safety approach is that the new food (or component thereof) should be compared with an appropriate conventional counterpart, that is with a food already accepted as safe based on its history of safe use as food. The assessment should follow a structured and integrated approach. It should evaluate both intended and unintended effects, that is, intended and unintended differences from the conventional counterpart; it should identify new or altered hazards; and it should identify any changes in key nutrients that are relevant to human health.

In the Guideline for the conduct of the food safety assessment of foods derived from recombinant-DNA plants the principles for risk analysis of foods derived from modern biotechnology are further detailed. For example, paragraph 4 of the Plant Guideline reiterates that rather than trying to identify every hazard associated with a particular food, a safety assessment should take a comparative approach and identify new or altered hazards relative to the conventional counterpart. Paragraph 5 of the Plant Guideline notes that if a new or altered hazard, a nutritional issue or other food safety concern is identified, one would then need to determine its relevance to human health. If all significant differences are identified and found not to pose safety concerns, then the new food can be considered to be as safe as its conventional counterpart.

The framework for conducting such a safety assessment is outlined in paragraph 18 of the Plant Guideline. It states that the safety assessment of a food derived from a recombinant-DNA plant follows a stepwise process of addressing relevant factors that include:

(A) Description of the recombinant-DNA plant
(B) Description of the host plant and its use as food
(C) Description of the donor organism(s)
(D) Description of the genetic modification(s)
(E) Characterization of the genetic modification(s)
(F) Safety assessment:
  (a) expressed substances (non-nucleic acid substances)
  (b) compositional analyses of key components
  (c) evaluation of metabolites
  (d) food processing
  (e) nutritional modification
(G) Other considerations

The reader can refer to the Plant Guideline itself for further details and pertinent discussion.

GMO risk assessment in the European Union – EFSA initiatives

In the European Union, Member States and EU institutions have agreed a legal framework for the authorization of GMOs. The two main legal instrument for GMO safety assessment are *Council Directive 2001/18/EC*, which provides the principles regulating the deliberate release into the environment of GMOs, and *Regulation (EC) 1829/2003* of the European Parliament and the Council, which strengthens and expands the rules for GMO safety assessment by introducing the 'one-key-one-door' approach, namely the need for one authorization to cover both food and feed uses.

Directive 2001/18/EC puts in place a step-by-step approval process made on a case-by-case assessment of the risk to human health and the environment before any GMO can be released into the environment, or placed on the market as, or in, products. The Directive introduces the obligation to propose a monitoring plan in order to trace and identify any direct or indirect, immediate, delayed or unforeseen effect on human health or the environment of GMOs as, or in, products after they have been placed on the market. According to *Regulation (EC) 1829/2003*, GM food and feed should only be authorized for placing on the market after a scientific assessment of any risk which they may present for human and animal health and, as the case may be, for the environment. The Regulation requires that GM food/feed must not (a) have adverse effects on human health, animal health or the environment; (b) mislead the consumer/user; (c) differ from the food/feed which it is intended to replace to such an extent that its normal consumption would be nutritionally disadvantageous for the consumer/animals.

The European Food Safety Authority (EFSA) has a central role in the independent scientific advice and risk assessment of GMOs, whereas the decision-making with respect to products authorization, inspection and control are the responsibility of the risk managers of the Member States and of the European Commission. The EFSA consults national competent authorities on every GMO application and provides feedback to scientific concerns that are raised by the Member States during the risk assessment process. The EFSA opinions are made available on the EFSA website (http://www.efsa.europa.eu). Subsequently, the European Commission organizes a public consultation before

proposing a draft authorization decision to the mandated Regulatory Committee.

The EFSA Scientific Panel on GMOs has developed guidance documents for the risk assessment of GM plants (EFSA, 2006a) and GM microorganisms (EFSA, 2006b). These guidance documents assist applicants in their preparation and presentation of marketing applications. The GM plant guidance document covers the full risk assessment of GM plants and derived food and feed. The risk assessment process consists of four steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, which culminates in (iv) an integrative risk characterization. The EFSA guidance, which is regularly updated, follows the specific EU regulatory requirements, and it is based on the comparative assessment approach as developed by the OECD (OECD, 1993) and further elaborated by FAO/WHO (FAO/WHO, 2000) and it is in line with the Codex recommendations (Codex Alimentarius, 2003).

Briefly, the EFSA guidance is based on a two-step logic: (1) identification of possible differences between the GM and non-GM crop, and (2) assessment of the environmental safety, the food/feed safety and the nutritional impact of the identified differences, if any. The guidance defines data requirements and it provides a detailed description of the issues to be considered when carrying out a comprehensive risk characterization. These include molecular characterization of the genetic modification, assessment of the modification with respect to the agronomic characteristics of the GM plant, and evaluation of food/feed safety aspects of the GM plant and/or derived food and feed. Data on composition, toxicity, allergenicity, nutritional value and environmental impact provide, on a case-by-case basis, the cornerstones of the risk assessment process. Key elements for the environmental risk assessment are potential changes in the interactions of the GM plant with the biotic and abiotic environment resulting from the genetic modification. The characterization of risk may give rise to the need for further specific activities including post-market monitoring of the GM food/feed and/or for the environmental monitoring of GM plants.

Recently, the GMO Panel has taken several initiatives to further advance the science of GMO risk assessment and to address specific scientific concerns. An overview of the different initiatives is described below.

The GMO Panel adopted a scientific opinion on the use of antibiotic resistance marker genes in GM plants (EFSA, 2004), which was further complemented with a statement concerning the safety of a specific marker gene: *npt*II (EFSA, 2007a), where it was concluded that the use of the *npt*II gene as selectable marker in GM plants does not pose a risk to human or animal health or to the environment.

Under the EU regulatory framework, a new application must be submitted when transgenic traits are stacked (*i.e.* combined) through the interbreeding of existing GM lines, a strategy which is increasingly being used to combine more and more traits into the so-called 'multiple stacked events'. Data on the single events are the basis for the risk assessment of stacks, and additional data are required to assess intended or possibly occurring unintended effects which could arise because of possible interaction/s of the stacked genes. The EFSA GMO Panel has developed a specific guidance for the risk assessment of stacked events to address these issues (EFSA, 2007b).

A debated topic in the EU regards the use of animal feeding trials for the risk assessment of GMOs. In particular the value of a subchronic 90-day rodent feeding study on whole food and feed has been the subject of scientific discussion. In 2005, the GMO Panel started considering in depth the potentials and limitations of animal feeding trials for the safety and nutritional testing of whole GM food and feed. This work resulted in an extensive report (EFSA, 2008), where it is concluded that subchronic 90-day rodent feeding study on whole GM plant derived food and feed has sufficient specificity, sensitivity and predictability to act as a sentinel study in order to detect toxicologically relevant differences, as well as nutritional deficiencies/improvements that may be due to the expression of new substances, or alterations in the levels of natural compounds. The report advises that toxicological testing with the whole GM food/feed should be carried out in case the composition of the GM plant is modified *substantially*, or if there are any indications for the occurrence of unintended effects based on a preceding analysis of the molecular characteristics of the GM organism and/or its agronomic, phenotypic or compositional properties.

Other ongoing work of the GMO Panel includes (1) the consideration of new approaches for the assessment of the potential allergenicity of GM food and feed with particular attention on the use of bioinformatics, *in vitro* tests and development of animal models; (2) the development of guidance for the risk assessment of GM plants for non-food or non-feed purposes (*e.g.* molecular farming); and (3) the consideration of strategies for statistical analysis of data generated for the comparative food safety evaluation of GMOs. In particular, the GMO Panel is investigating whether more detailed guidance could be provided to applicants regarding the performance of field trials and statistical analysis of collected data.

EFSA is also giving attention to specific issues of the environmental risk assessment of GM plants which still needs further development such as environmental fitness, effects on non-target organisms, long-term and large-scale environmental effects, broader environmental considerations and the assessment of risk *versus* environmental benefit. The current case-by-case tiered approach to environmental risk assessment, as outlined in EFSA's guidance document, is recognized to be very effective; however more specific guidance is needed to assess the potential impact on non-target organisms. The GMO Panel is currently developing more detailed guidance to assess the impact of GM plants on non-target organisms.

Post-market environmental monitoring (PMEM) of GMOs is mandatory in all applications for deliberate release submitted under *Directive 2001/18/EC* and *Regulation (EC) 1829/2003*. The PMEM of the GM plant has two aims: (1) to study any possible adverse effects of the GM plant identified in the formal pre-market risk assessment procedure, and (2) to identify the occurrence of adverse effects of the GMO or its use which were not anticipated in the environmental risk assessment. PMEM is composed of case-specific monitoring and general surveillance. The GMO Panel provides guidance for general surveillance of unanticipated adverse effects of the GM plants in the EFSA guidance for the risk assessment of GM plants (EFSA, 2006a).

In summary, the European Union has developed a rigorous and detailed framework for the risk assessment of GMOs, which is in line with internationally agreed procedures. EFSA will continue to further advance the science of risk assessment, update its guidances accordingly, and strengthen co-operation with other national organizations experienced in risk assessment of foods/feeds.

Risk assessment of plants derived from biotechnology: The US approach

Under US law, food that is adulterated or misbranded may not be introduced or delivered for introduction into interstate commerce (Section 301 of the Federal Food, Drug, and Cosmetic Act – FFDCA http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm). Adulterated food is defined in part as food that contains any poisonous or deleterious substance that may render it injurious to health, or that contains an unsafe food additive or unsafe pesticide residue (Section 402, FFDCA). An unsafe food additive is one that has not been used according to an authorizing regulation (Section 409, FFDCA). An unsafe pesticide residue is one that has not been granted a tolerance or tolerance exemption (Section 408, FFDCA). The Food and Drug Administration (FDA) has oversight of food additives and the Environmental Protection Agency (EPA) has oversight of pesticides. The implication for biotechnology-derived foods is that if they contain a food additive or pesticide, that food additive or pesticide must have gone through the relevant pre-market authorization procedure by FDA or EPA before the biotech food could be marketed. However, if they do not contain a food additive or a pesticide, they are not subject to any pre-market approval requirement. The fact that a plant was developed using rDNA techniques is not itself a regulatory trigger for food safety oversight or pre-market approval http://www.cfsan.fda.gov/~acrobat/fr920529.pdf.

The FFDCA defines a food additive essentially as a substance whose intended use may reasonably be expected to result in its becoming a component of food or affecting the characteristics of a food, but that is not a pesticide or new animal drug, and is not generally recognized as safe (GRAS) by qualified scientific experts under the conditions of its intended use (Section 201, FFDCA). To date, virtually all new substances introduced into food by biotechnology that are not pesticides have been considered by FDA to be presumptively GRAS, and so have not been subject to food additive approval.

Apart from the presence of food additives or pesticides, foods (biotechnology-derived or otherwise) are still subject to post-market oversight. For example, if a biotechnology-derived food were to contain elevated levels of a native toxicant, such that the food was unsafe, the food would be adulterated and so illegal (Section 402, FFDCA). Or if the composition of the food was changed in a manner such that the food would need to be labeled to indicate that it was different from the usual food with which it would otherwise be confused, the absence of such labeling would render the food misbranded and so illegal. The FFDCA gives FDA broad authority to initiate legal action against a food that is adulterated or misbranded within the meaning of the Act.

FDA has a voluntary consultation process for foods and feeds from new plant varieties, described in a guidance available at http://www.cfsan.fda.gov/~lrd/consulpr.html. The consultation process, although voluntary, has proved to be valuable for developers of food crops using modern biotechnology to resolve questions related to the safety and regulatory status of their foods. As a result, FDA is not aware of any biotechnology-derived food, intended for commercialization in the US market that has not been the subject of a consultation with FDA prior to marketing.

Through the consultation process, developers or firms intending to commercialize a new plant variety for food or animal feed use submit to FDA a safety and nutritional assessment summary containing sufficient information for FDA scientists to understand the approach the firm has followed in identifying and addressing relevant issues. The FDA considers a consultation to be completed when FDA no longer has questions about the firm's evaluation of the safety and regulatory issues. At that point, it provides a letter to the firm stating that it has no further questions about the food or feed from the new plant variety. FDA publishes on its website the letter and a technical memo describing the information it evaluated (http://www.cfsan.fda.gov/~lrd/biocon.html).

FDA recommends that a consultation ordinarily includes the following information:

1. The name of the bioengineered food and the crop from which it is derived.
2. A description of the various applications or uses of the bioengineered food, including animal feed uses.
3. Information concerning the sources, identities, and functions of introduced genetic material.
4. Information on the purpose or intended technical effect of the modification, and its expected effect on the composition or characteristic properties of the food or feed.
5. Information concerning the identity and function of expression products encoded by the introduced genetic

material, including an estimate of the concentration of any expression product in the bioengineered crop or food derived thereof.
6. Information regarding any known or suspected allergenicity and toxicity of expression products and the basis for concluding that foods containing the expression products can be safely consumed.
7. Information comparing the composition or characteristics of the bioengineered food to that of food derived from the parental variety or other commonly consumed varieties with special emphasis on important nutrients, and toxicants that occur naturally in the food.
8. A discussion of the available information that addresses whether the potential for the bioengineered food to induce an allergic response has been altered by the genetic modification.
9. Any other information relevant to the safety and nutritional assessment of the bioengineered food.

While using somewhat different language, the elements listed above are essentially the same as those recommended for assessment in paragraph 18 of the Codex Guideline. Like Codex, FDA recommends that the new food be compared to an appropriate counterpart, and that intended and unintended changes be identified and their safety determined. New proteins expressed in the food should be assessed for potential toxicity and allergenicity, and the composition of the food should be evaluated, relative to an appropriate comparator, for possible changes in the levels of important nutrients and known toxicants.

As noted above, pesticides introduced into plants by biotechnology are subject to the same FFDCA mandatory pre-market requirements as applicable to conventional pesticides. Such pesticides (including the pesticidal substance, such as a *Bacillus thuringiensis* delta-endotoxin protein, and the genetic material necessary for its production), are together referred to as ''plant incorporated protectants, or PIPs. EPA sets a tolerance level for the pesticide in food (the maximum level at which the pesticide is considered to be safe) or issues an exemption from the requirement of a tolerance for the pesticide because no tolerance level is needed to assure food safety. In the case of PIPs in biotechnology-derived plants, EPA has authorized an exemption from the requirement of a tolerance in all cases to date (http://usbiotechreg.nbii.gov).

As part of its safety review of PIPs, EPA requires direct testing of the pesticidal substance, typically a protein, in an acute oral toxicity study performed on rats or mice. This test is a maximum hazard dose analysis of the protein, intended to uncover any evidence of acute toxicity as observed over a 14 day period. Parameters measured include individual weight gain or loss, behavioral indicators, individual organ weights, any notable pathology upon gross necropsy, and mortality.

In addition to the acute toxicity study, EPA requires assessment of toxicity and allergenicity of the pesticidal protein through comparative database searches for amino acid homologies to known toxins and allergens, *in vitro* gastric simulation of digestibility and a heat stability examination. The data and information required are consistent with that recommended in the Plant Guideline and allergenicity annex.

Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA – http://www.epa.gov/opp00001/regulating/fifra.pdf), plants containing PIPs must receive an EPA registration or experimental use permit before they may be grown in field trials at greater than 10 acres (four hectares) cumulative area. EPA requires information on the plasmid construct used in transformation of the plant, transformation procedures, number of inserts, stability, heritability, DNA sequence, origin of the sequence, expression levels of the pesticidal trait in various plant tissues, and descriptive biology of the source organism and recipient plant (including potential for weediness and invasiveness, and presence or absence of naturally occurring sexually compatible relatives). EPA also requires toxicity assessments for potential environmental impacts, using bird, fish, aquatic invertebrate, insect and estuarine or marine species.

The Animal and Plant Health Inspection Service (APHIS) of the US Department of Agriculture has a complementary role over plants developed using rDNA technology. Under the Plant Protection Act (http://www.aphis.usda.gov/brs/pdf/PlantProtAct2000.pdf), APHIS is responsible for protecting agriculture from pests and diseases. Accordingly, APHIS regulates organisms and products that are known or suspected to be plant pests or to pose a plant pest risk, including those that have been altered or produced through genetic engineering. These are called ''regulated articles.'' APHIS regulates the import, handling, interstate movement, and release into the environment of regulated organisms that are products of biotechnology, including organisms undergoing confined experimental use or field trials. Regulated articles are reviewed to ensure that, under the proposed conditions of use, they do not present a plant pest risk through ensuring appropriate handling, confinement and disposal.

APHIS regulations provide a petition process for the determination of non-regulated status. If a petition is granted, that organism will no longer be considered a ''regulated article'' and will no longer be subject to oversight by APHIS. The petitioner must supply information such as the biology of the recipient plant, experimental data and publications, genotypic and phenotypic descriptions of the genetically engineered organism, and field test reports. APHIS evaluates a variety of issues including the potential for plant pest risk; disease and pest susceptibilities; the expression of gene products, new enzymes, or changes to plant metabolism; weediness and impact on sexually compatible plants; agricultural or cultivation practices; effects on non-target organisms; and the potential for gene transfer to other types of organisms. A notice is filed in the US Federal Register and public comments are considered on the environmental

assessment or environmental impact statement and determination written for the decision on granting the petition. APHIS makes available to the public the APHIS environmental review documents as well as a non-confidential copy of the documentation submitted by the person petitioning APHIS for non-regulated status.

In the US, ''stacks'' (plants containing multiple rDNA traits as a result of conventional breeding among rDNA plants containing different rDNA traits) generally do not receive additional evaluation when the individual traits have successfully completed the FDA, APHIS and EPA procedures. However, plant lines with more than one PIP do need a separate FIFRA registration from EPA for growth on greater than 10 acres, because the combined PIPs would constitute a new pesticide.

Regulation of novel foods in Canada

The globalization of the food supply, the demand for more food sources globally, and the rapid advances in food science and technology have resulted in the introduction of foods not previously available in the marketplace. Novel whole foods and food ingredients may appear through the importation of new products, the introduction of a new species as a food source, the use of new processing techniques, and/or changes in the genetic make-up of the microorganisms, plants and animals from which foods are derived.

In response to these developments, Health Canada promulgated the *Novel Foods Regulation* under the *Canadian Food* and Drugs Act on October 27, 1999 (http://www.hc-sc.gc.ca/fn-an/legislation/acts-lois/fdr-rad/division-titre28_e.html). This regulation requires the mandatory pre-market notification of foods intended for sale in the Canadian marketplace that were not previously available or have been modified from their traditional counterpart. Manufacturers and importers are required under these regulations to submit information to Health Canada regarding the product in question so that a determination can be made with respect to its acceptability as food prior to sale. Under the *Novel Foods Regulation* a ''novel food'' is defined as follows:

(A) A substance, including a microorganism that does not have a history of safe use as a food
(B) A food that has been manufactured, prepared, preserved or packaged by a process that
  (i) has not been previously applied to that food
  (ii) causes the food to undergo a major change
(C) A food that is derived from a plant, animal or microorganism that has been genetically modified[1] such that
  (iii) the plant, animal or microorganism exhibits characteristics that were not previously observed in that plant, animal or microorganism,
  (iv) the plant, animal or microorganism no longer exhibits characteristics that were previously observed in that plant, animal or microorganism,
  (v) one or more characteristics of the plant, animal or microorganism no longer fall within the anticipated range for that plant, animal or microorganism.

[1] ''Genetically modify'' means to change the heritable traits of a plant, animal or microorganism by means of intentional manipulation.

Regulatory oversight for novel foods in Canada is triggered by the new characteristics of the product rather than the process used to create the product. Potential food safety issues are those associated with toxins, contaminants and anti-nutritional factors that could be introduced into the food supply *via* the importation of new products, the introduction of a new species as a food source, the use of new processing techniques, or changes in the genetic make-up of organisms. To date, Health Canada has authorized the sale of over 100 novel foods (http://www.hc-sc.gc.ca/fn-an/gmf-agm/appro/index_e.html) following a thorough safety assessment of each product. Examples of novel foods approved include: food ingredients such as trehalose and vegetable diacylglycerol oil that did not have a history of safe use; new processes, such as high hydrostatic pressure treated ready-to-eat meats and UV treated apple juice and cider that resulted in a major change in the microbiological safety of these products; and foods derived from genetically modified plants exhibiting new characteristics such as herbicide tolerance and insect resistance.

Given the wide variety of novel foods and the many reasons why a food could be classified as novel, the amount of information necessary for the safety assessment can vary widely from one case to another.

The degree of regulatory oversight necessary for novel food products in Canada is based on the potential risks posed by the product in comparison to its conventional counterpart, where applicable. A risk-based approach is used by Canadian regulatory authorities to protect the consumer while not imposing unnecessary burden on the government and the industry for products that are not truly ''novel'' food products.

In the case of new plant varieties being proposed for the marketplace, the regulatory trigger is related to the introduction or change in characteristics not previously observed in that plant. Examples include the introduction of new proteins and significant changes in composition.

As mentioned, the characteristics of the new plant variety or final food product derived from that plant determines the need for a pre-market assessment, not the process used to introduce or alter these characteristics. This is based on the fact that many of the issues raised by foods resulting from recombinant-DNA (rDNA) technology (*e.g.* introduction of new compounds or unintentional compositional changes) are equally applicable to foods produced by conventional breeding techniques such as mutation breeding.

The following two examples of novel rice lines illustrate the product-based approach for evaluating novel foods.

In the first case, a rice line was developed through chemical mutagenesis, which caused a genetic change that resulted in an alteration to the acetohydroxy acid synthase (AHAS) protein. This mutation allows the plant to grow in the presence of imidazolinone herbicides. In the second case, a rice line was developed using biolistics to introduce the *Streptomyces hygroscopicus bar* gene and regulatory components necessary for expression. Expression of the *bar* gene confers tolerance of glufosinate ammonium herbicides. Both of these rice lines were considered a novel food since these rice plants were genetically modified to exhibit new characteristics not previously observed in rice. In both cases, the safety assessment conducted by Canadian regulatory authorities evaluated the new characteristic introduced and the potential for unintended changes in the nutritional and toxic characteristics of the food product.

Canada's approach to novelty can be viewed as a unique regulatory requirement that can differ from the international standard, especially in the case of non-rDNA or traditionally bred plants. The product-based trigger for regulating new plant varieties in Canada is broader than the process-based system currently used in other jurisdictions due in large part to how genetic modification is defined in the *Novel Foods Regulation*. However, this approach provides equal regulatory oversight for all developers since any new plant variety, regardless of the genetic modification method used to produce the plant, could pose a risk by the introduction of toxic compounds or changes in the composition of the food product.

In recent years, developers of new plant varieties and other stakeholders have asked Canadian regulatory authorities to clarify the use of novelty as the regulatory trigger. Health Canada's Food Directorate is moving towards activities to strengthen the risk-based approach to allocating regulatory resources to the pre-market assessment of novel foods to streamline the assessment process for low-risk products. This will involve improving the efficiency of the pre-market assessment process, clarifying novelty triggers, and developing a tiered approach to food risk assessment. Canadian regulatory authorities will continue to seek out opportunities to align the regulatory approach for novel foods with international best practices and harmonize with other nations or international organizations.

Additional information is available at the Health Canada's novel foods website: www.novelfoods.gc.ca.

GMO environmental risk assessment – The Australian approach

Although there are considerable differences between countries in regulatory structures, environmental priorities (including the preservation of endemic biodiversity) and risk terminology (Hill, 2005), most environmental risk assessments of GMO releases use some form of science-based assessment process that estimates the level of risk through comparison with a non-GM counterpart. In addition, most involve consideration of a range of issues relevant to the overall risk assessment. For GM plants, depending on the introduced trait, these may include toxicity, allergenicity, nutritional profile, agronomic characteristics, increased disease burden, spread and persistence of the GMO, gene flow etc.

This section describes some of Australia's regulatory experiences with GM plant releases into the environment. Detailed information on the structure of the integrated regulatory framework which involves coordinated decision making by regulatory agencies with complimentary responsibilities, and the assessment processes used by the Gene Technology Regulator (the Regulator) is available in the *Risk Analysis Framework* (OGTR, 2007).

Under the *Gene Technology Act 2000* (http://www.ogtr.gov.au/pubform/legislation.htm), all intentional environmental releases of GMOs, *i.e.* both field trials and commercial releases, must be licensed. The former are required to be conducted under mandated limits that restrict their size, location and duration, and control measures that are designed to prevent the dissemination and persistence of the GMOs and their introduced genes. The trigger for regulation is the use of gene technology and decisions on whether to issue licenses are based on comprehensive, case-specific, science-based risk analyses. These include consideration of uncertainty in the risk assessment and its potential impact on the risk management measures that might be imposed as license conditions.

Australia has gained the most regulatory experience with GM cotton. The first releases occurred in 1996 under a voluntary oversight system administered by the Genetic Manipulation Advisory Committee. In the seven years since the legislation was introduced in 2001, the Regulator has issued a total of 59 licenses, 50% of which are for GM cotton lines incorporating a diverse range of traits. Of the 10 commercial release licenses, six are for a range of insect resistant and/or herbicide tolerant GM cottons (the others are for GM carnation, GM cholera vaccine, and two GM canola). In addition, Food Standard Australia New Zealand (FSANZ) approved the use of oil and linters from the GM cottons for use in food, and the Australian Pesticides and Veterinary Medicines Authority (APVMA) registered the use of the relevant herbicides on the herbicide tolerant GM cottons and the insecticidal proteins produced by the insect resistant GM cottons. Further information is available from www.ogtr.gov.au/gmorec/ir.htm#table.

After more than 10 years since the commercial release of the first GM cotton line, while some of the original lines have been superseded, more than 90% of the Australian cotton crop is now genetically modified. This has resulted in a number of agronomic changes of significance for future risk assessments of environmental release applications. For instance, the original comparator for GM cotton was non-GM cotton. However, now that the majority is GM, the non-GM parent cotton plant is no longer sufficient as the sole baseline comparator. In addition, the cotton industry has reported a substantial decrease in the use of insecticide

on cotton crops with associated effects on biodiversity, including increases in the abundance of certain non-target organisms, such as pollinators (*e.g.* Whitehouse, Wilson, & Fitt, 2005).

Australia has also gained experience in managing the threat of resistance developing to the insecticidal proteins expressed in the GM cotton plants or as a result of transfer of the herbicide tolerance genes. Resistance development is considered to be a product efficacy issue, rather than an environmental risk, and is managed by the APVMA which regulates the use of all agricultural chemicals under the *Agricultural and Veterinary Medicines Act 1994*. Resistance to insecticides is managed by the APVMA and the cotton industry through conditions placed on the product registration for the use of refugia (to mitigate selection pressure), non-chemical control methods and monitoring for the evolution of resistance. The development of herbicide resistance in weeds is addressed through 'Best Practice' guidelines that incorporate integrated management strategies including rotation of herbicides and mechanical weed control methods. These measures are subject to continuous review by an advisory group comprising industry, academic and state government agricultural representatives.

The complexity of environmental risk assessments will increase in the future. While considerations for limited and controlled field trials often focus on the effectiveness of the containment measures, other issues arise where releases with fewer limits and controls are proposed. For instance, the greater the number of GM traits released, the greater the number of novel crosses between these GM plants that will occur (either intentionally or unintentionally). Companies are already projecting releases of more complex, deliberate stacks with around six or more traits combined into a single plant. The possibility of different combinations of GM events as a result of crossing must be included in risk assessments to evaluate the potential human and environmental impacts, and to prevent unauthorized GMOs resulting from these crosses.

In order to maintain appropriate ongoing oversight of commercial releases the Regulator has introduced a mechanism for case-by-case implementation of a program of post-release review (PRR). PRR enables a cautious approach to continue during a release, providing valuable feedback into the risk assessment process and enabling appropriate responses to changing circumstances. License holders are also obliged to advise the Regulator of unexpected or adverse effects. Reports of adverse effects on people or the environment can also be made through a third party reporting system.

Increases in the international trade of GMOs and GM products will also increase the potential for the unintended presence of GMOs in grain shipments that have been approved asynchronously in different jurisdictions. As a result, the Regulator is working with other relevant government agencies and industry to implement a national strategy to manage the unintended presence of unapproved GMOs in imported seeds for sowing.

Consultation is an important component of the operation of Australia's regulatory system, providing opportunities for a wide range of stakeholders, including the public, to provide input. Ensuring that the risk analysis methodology and processes used are transparent and understandable to all stakeholders enables increased participation and is intended to instill greater confidence in and ownership of regulatory decisions.

Finally, efforts are being made to more effectively incorporate the accumulated knowledge and experience of conventional (non-GM) agriculture and breeding into enhanced risk assessments and the design of effective containment measures for GMOs. A current initiative is to apply nationally accepted standards in weed risk assessment.

The Office of the Gene Technology Regulator participates actively in international efforts that aim to harmonize risk assessments for environmental releases of GMOs and FSANZ is significantly involved in the Codex Taskforce.

Conclusions

A comparison of the mandatory GMO risk assessment strategy implemented by the EU with the voluntary food safety consultation process in the USA, or with the Canadian requirement for a risk assessment of any novel food products shows that a general agreement exists as laid down in Codex (Codex Alimentarius, 2003) where the principles have been developed and accepted. The foundation is the comparative assessment, namely the comparison of the GMO (and/or its derived product/s) with its best conventional counterpart, *i.e.* a non-GM organism with the closest genetic background to the GMO under assessment, which has gained a history of safe use. The conclusion of this comparison is a risk characterization which should provide an informed scientific guidance for the decision-making process of risk managers.

Experience with environmental risk assessments of GMOs is more limited, and the implementation of international harmonization less advanced than for GMO food/feed risk assessments. Yet, the evaluation of the environmental impact of GM crops relative to the parent plant(s) forms a cornerstone of regulatory decision-making in most jurisdictions and initiatives, ranging from multi-lateral to bilateral, provide important forums for advancement. For example, the Organization for Economic Co-operation and Development (OECD) and the United Nations Environment Program have specific initiatives to provide guidance and to support harmonization across countries. The OECD also publishes resource materials in the form of consensus documents on the biology of different plant species (http://www.oecd.org/document/51/0,3343,en_2649_34385_1889395_1_1_1_1,00.html) for use as a common basis in the conduct of assessments. In the European Union, EFSA organized a dedicated Colloquium to discuss approaches to environmental risk assessment in the light of current scientific thinking and knowledge. Regulatory officials of the US and Canada, recently joined by officials from Mexico,

hold regular technical discussions on environmental reviews of rDNA plants, focusing on molecular genetic characterization and environmental interactions. Canada and the US published two documents describing their approaches to these issues (http://www.inspection.gc.ca/english/plaveg/bio/usda/appenannex1e.shtml, and http://www.inspection.gc.ca/english/plaveg/bio/usda/appenannex2e.shtml) and are working with Mexico to update these documents.

Although there is an international consensus recognizing comparative assessment as the core principle for GMO risk assessment, there are still differences in the triggers needed to start the risk assessment itself across countries. In the EU, risk assessment is required for GM foods/feeds and the deliberate release into the environment of organisms which have been genetically modified. Australia also applies this process-driven approach to the evaluation of all applications for intentional release of a GMO, whereas in the US both biotechnology-derived and non-biotechnology-derived products are regulated according to their possible impact on the environment. In Canada the focus is on novelty, *i.e.* risk assessment is carried out according to the characteristics of a product, regardless of the technology used for its development and production (product-based approach).

Even in the frame of our limited comparison of risk assessment strategies in different countries it is evident the need for further harmonization and standardization of approaches with respect to specific issues such as design of field trials, data requirements including the use of animal experiments, and statistical approaches used for data evaluation. The EU is making efforts in this direction with *ad hoc* activities (see EU section for further details), but an international consensus is needed to further progress. Harmonization would enhance confidence in the quality and predictability of regulatory processes and benefit trade in food and feed commodities, particularly in view of the globalization of trade and the increasing development and cultivation of GM crops outside the EU.

Our hope is that the limited comparison of GMO risk assessment strategies summarised here can represent a first step towards the recognition of an international consensus. We appreciate that many more steps are needed before harmonization and standardization can be reached, especially with respect to standardization of the assessment of GMO environmental impacts. However, all these efforts will provide a basis for the further development of mutually recognized detailed guidelines for the design and execution of risk assessments of GMOs and derived food and feed products.

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