Introduction to the Safety/Risk Assessment of GM Crops [1]

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Summary

Using the tools of modern biotechnology to create genetically modified (GM) crops constitutes a real revolution in plant breeding. These techniques and products are generally regarded as highly novel, and hence require careful evaluation before commercial use. There is a worldwide consensus that this evaluation must be firmly grounded on empirically-based scientific risk/safety assessment. This review describes risk assessment, focuses on its role in the decision-making process, and also describes the major areas of concern for the present generation of GM crops.

Keywords: GM crops; Risk analysis; Risk assessment; Risk management; Comparative analysis.

1. Introduction

Agriculture has evolved to produce and select plants with more desirable traits. The advent of modern recombinant DNA technology has allowed for the introduction of DNA from any source into plant species. Currently, the majority of commercialised genetically modified (GM) crops [4] have been produced to enhance agronomic performance by transformation with genes encoding herbicide tolerance or pest resistance (James, 2006). However, the potential of GM plants is not limited to agronomic enhancement but may also serve as a means of enhancing the nutritional status of food for human consumption (Bouis *et al.*, 2003). The risk assessment (RA) of agricultural and food technologies is not a new concept. Each innovation in food production has come with its own set of potential risks. These have ranged from increased pesticide exposure in conventional agriculture to higher pathogen exposure from organic farming (Stewart *et al.*, 2000). All cultivated GM varieties have been formally assessed for safety by the competent authorities in the countries in which they are grown. Most countries have specific legislation requiring an objective empirically-based scientific assessment of identified or ascertainable potential health or environmental risks posed by specific products to be made, and detail the approach to be taken. In general, these RAs have been much more stringent than for conventionally produced crops and food. Furthermore, the scientific RA lies at the heart of a wider analysis which determines the acceptability of a given level of risk, based upon the evaluation of any economic, political, moral and ethical concerns that may be associated from using the technology (Johnson *et al.*, 2007).

2. Risk Analysis

Although the consideration of various sorts of risk is a daily occurrence in an ever more risk-averse society, there is often confusion between risk assessment and risk analysis. The former is the scientific evaluation of the probability of an undesirable event, whereas the latter reflects both scientific and rational non-scientific concerns, and encompasses not only the assessment, but also the management and communication of risk, including the production of management goals and threshold values, and the communication of the risk decision. Therefore, a science-based RA and a more broadly-based risk analysis and risk management decision are two distinct but related disciplines involving different experts and considerations (WTO, 2006). Should the RA identify sources of potential harm, assessing the likelihood that harm will occur and the consequences if harm does indeed occur, then the risk analysis process considers if the risk can be acceptably managed. Risk management involves selecting and implementing the plans or actions that are required to ensure that those risks are controlled. Essential to the overall process is risk communication through an interactive dialogue between stakeholders and risk assessors and risk managers. It is worth reiterating that the result of the scientific RA is not the decision whether or not to permit the cultivation of a GM crop. A decision will be made based on the amount of risk that is acceptable (the threshold value) if the crop is permitted to be cultivated, and, just as importantly, the risks of not permitting cultivation. For example, in circumstances where the status quo involves a high level of adverse health or environmental impact, the introduction of products or practices with a given level of risk may prove acceptable if they lead to a reduction in adverse impacts. The acceptability of a given risk therefore cannot be determined purely scientifically: science can predict the likelihood of certain effects, but non-scientific criteria must be included in the process of judging their acceptability (Johnson *et al.*, 2007). It has been further argued that even some of the basic concepts of risk assessment itself, specifically hazard identification, exposure modelling, and choice of comparison populations (see section 2.1.), each involve value judgments that are ethical or pragmatic but in either case cannot be characterised as following from established scientific findings or

1. Recently, major stakeholders have begun to refer to the risk assessment of GMOs as an overall safety assessment, in order to avoid the negative connotations that the public perceives with the word risk . However, this terminology has yet to be precisely defined and widely adopted.
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4. Variously referred to as genetically engineered , genetically manipulated , genetically modified , and transgenic .

theories (Jensen *et al.*, 2003; Thompson, 2003 and Wilkinson & Ford, 2007). As previously stated, the specification of management goals in legislation reflects societal concerns. Specific assessment endpoints , such as the preservation of populations or habitats of rare species within the agro-ecosystem (as opposed to nature reserves) and the extent to which the public are prepared to pay for the non-food component of agriculture (Hails, 2002), or the continuation of trade in foreign commodity markets, are also reflections of what society considers important.

2.1. Risk Assessment:

Carrying out environmental and health (human and animal) RAs is a requirement under international and national legislation before any GM crop variety can be cultivated commercially, or their derived products can enter the market. The current RA of GM crops for food, feed, and environmental applications is rigorous, and consensus has been achieved through dialogue at various international fora (CODEX, 2004; FAO/WHO, 2007 and OECD, 2007a & b). Assisting this process has been the definition of the key terminology central to risk analysis (European Commission, 2000 and US EPA, 2007).

In practice, an RA is an iterative process that involves proceeding through several steps of assessment prior to obtaining results with an acceptable level of uncertainty (Craig *et al.*, 2008). For example, how might the proposed activity, in this case the cultivation or consumption of GM crops, affect components (or assessment endpoints) of the environment or health about which we are concerned? To answer this question, particularly with respect to quantifying or predicting any risk, requires a multitude of different scientific disciplines and their effective coordination. A committee comprising scientists (e.g. ecologists, geneticists, plant breeders, toxicologists) usually assesses data (test endpoints) on the hazard and exposure of the crop in order to predict the risk to the assessment endpoints. The data in question might already exist or need to be generated by new studies undertaken at the request of the competent authority.

Risk has generally been formulated as:

Risk = *f* (hazard, exposure), in which hazard is the undesired effect, and exposure the probability or likelihood of its occurrence.

For risk to be properly assessed, both hazard and exposure need to be quantified for the risk assessment to have a high level of quantitative power. A thorough understanding of the pertinent variables is necessary in order to manage, communicate and mitigate any risks of GM crops, and this requires detailed scientific studies. The hazard and/or the exposure can be reduced to minimise risk, but formally it is impossible to totally eliminate risks. Therefore, if the operating regulatory process incorporates the precautionary principle, it is important to ensure that all of the risks associated with not adopting the GM plant are also included in any decision-making process (Poppy, 2004).

In practical terms, an RA may begin with initial laboratory experiments which mimic worst-case scenario conditions, for example by exposing non-target organisms to a stressor at elevated (acute) doses. Where a hazard has been substantiated (and if the degree of risk or uncertainty is deemed unacceptable), the RA proceeds to more realistic hazard and exposure scenarios. This is often referred to as a tiered approach (Raybould & Cooper, 2005). According to this approach, if the initial studies show the absence of a hazard with sufficient certainty, the assessment can be terminated. Thus, expensive full RAs are only implemented for hazards that are deemed possible under realistic conditions. Although this approach appears quite logical and straightforward, it does pose problems. There is the danger that a potential hazard can be overlooked, and also the simulation of changes to the community or broader ecosystem is prone to difficulty (Wilkinson, 2004). In fact, it is quite a challenge to design worst-case laboratory conditions that provide results that can be extrapolated to realistic field conditions with sufficient certainty (Lövei & Arpaia, 2005).

Notably, hazard does not automatically equate to risk unless exposure is also demonstrated. The case of the Monarch butterfly provides an excellent example of how an RA works when a hazard has been detected. Toxicological (hazard identification) studies established the sensitivity of Monarch larvae to consuming Cry1Ab protein from Bacillus thuringiensis (Bt) expressed in transgenic maize (Losey *et al.*, 1999), thereby triggering further RA studies to assess exposure and population level effects (Sears *et al.*, 2001 and Dively *et al.*, 2004). It was determined that larval exposure to pollen on a population-wide basis was low, given the proportion of larvae in maize fields during pollen shed, the proportion of fields planted in Bt maize, and the levels of pollen within and around maize fields that exceed the toxicity threshold (Oberhauser *et al.*, 2001 and Pleasants *et al.*, 2001). However, an acute dose, even if several times higher than would be expected in the field, is not equivalent to a low natural chronic dose experienced over a longer period, therefore a two-year study was undertaken, and subsequently demonstrated that the risk to Monarch butterfly populations is 0.6% of the total of Monarch butterflies breeding in the North American Corn Belt (Dively *et al.*, 2004). These results indicated negligible effects of Bt pollen to Monarch butterfly larvae from extended exposures in field settings.

2.2. Risk Management:

The risk management component of risk analysis builds on the work of the RA and may be described as answering the questions: Does anything need to be done about the risk, and what can be done about it? While RA deals as far as possible with objective evidence, risk management necessarily involves careful judgements about which risks require management (risk evaluation), the choice and application of management measures, and ultimately whether regulatory authorisation is advisable. Consequently, if there is uncertainty about risks (e.g. in early stage research) this may influence the management measures that are selected.

A consideration of the causal pathways for harm to occur that were elucidated in the RA provides a basis for strategic selection of how, where and when to undertake risk management measures. This enables the identification of the

points at which treatment can be most effectively applied to break the causal pathway and prevent adverse outcomes from being realised. While the focus of risk management is on prevention, it can also address how to manage adverse outcomes if a particular risk is realised. Important considerations are whether the adverse consequences can be reduced or reversed, identifying measures that can achieve these ends, and including these in authorising conditions or contingency plans (OGTR, 2005).

3. Areas of Concern

Potential risks posed by a particular GM crop are usually considered in the context of the known risks posed by the unmodified parental organism in the receiving environment (EFSA, 2004). Therefore, an RA typically comprises detailed comparisons of the GM crop composition and performance with those of their conventionally-bred counterpart under both field and glasshouse conditions, as well as of derived product composition and properties (Shewry *et al.*, 2007). Specifically required data include molecular characterisation at both the DNA and protein expression levels, along with comparative data of agronomic performance, environmental interactions, compositional analyses and wholesomeness studies (based on various animal feeding experiments). Areas of concern that are evaluated during the RA fall into two broad categories:

- the potential of the GMO to be harmful to humans and other organisms, and
- the potential of the GMO to adversely affect any ecosystem.

3.1. Baseline Characterisation of the Crop:

The RA of a GM crop requires a precise characterisation of the introduced genetic elements, information on which genes are expressed in the modified plant, and evidence that no detectable unintended effects have occurred because of the insertion. It is also necessary to confirm that the transgenes behave similarly to endogenous genes in their stability and inheritance between generations. Obviously, the GM and non-GM counterpart should differ in respect to the expression of the transgenes, but there should also be no unexpected knock on effects on the expression of other genes. Comparative analyses have the potential to identify unintended effects resulting from the transformation process (e.g. synergistic or antagonistic interactions between the transgenic and endogenous proteins). If statistically significant differences are found with the comparator, the impact of these changes should be further assessed to determine their biological significance. It is also important to ensure that the GM crop is equivalent in its functional properties and, in particular, the stability of these from year to year and across environments. Agronomic, phenotypic and compositional data are generally collected from field trials carried out in a range of agricultural environments that are typical of the place where the crop is grown. Agronomic performance studies include evaluations of plant vigour, growth habit, yield, crop quality, and insect and disease susceptibility.

3.2. Environmental Issues:

Managing the environmental effects of agriculture should be based on an assessment of biodiversity risks and benefits for all new agricultural practices, including the introduction of GM crops and the associated changes in crop husbandry (Hails, 2002 and ACRE, 2006). The environmental RA of a GM crop is based on the characteristics of the crop species, the genetic modification, the intended release or use, the potential receiving environment and the interaction between these (European Commission, 2002). The RA has traditionally been divided into direct and indirect impacts i.e. direct impacts arising from the presence of the transgenic plant itself, or the consequences of transfer of the transgene into wild relatives, as well as indirect impacts arising from the management practices associated with the transgenic crop (Hails, 2002).

3.2.1. Direct Impacts: The potential direct impacts of a GM crop include any changes in ecological fitness which may make the crop plant more prone to volunteerism (an agriculture problem where uncollected seeds from the last year s crop germinate and grow within the current crop) or any crop plant/wild relative hybrids more invasive, and will depend on the nature of the transgene, as well as the location and the management of its cultivation (Ellstrand *et al.*, 1999 and Ervin *et al.*, 2000). Crucially, host plants expressing transgenes that provide fitness-enhancing characteristics under natural conditions have the greatest potential to disrupt the balance of established ecosystems, due to their selective advantage (i.e. increased fitness) over other plants in the prevailing environment (Stewart *et al.*, 2000). For instance, if the transgenic trait is for enduring resistance to pathogens, drought, or temperature extremes, the host plant and its progeny could encroach upon and even replace populations of nearby wild relatives, but this would only occur if the species' population size is regulated by those same stressors. Additional impacts considered are those affecting non-target organisms which, from an agronomic point of view, are those that are associated with the crop but which do not cause economically relevant levels of damage (Sanvido *et al.*, 2007). For the current GM crops, it is generally accepted that toxic effects on non-target organisms are restricted to GM crops expressing insecticidal proteins (Conner *et al.*, 2003), of which only those with Bt proteins are marketed (James, 2006). In order for Bt crops to directly affect non-target organisms, the transgene product must be taken up either by direct feeding on the plants (e.g. leaf, pollen, phloem), be passed on in a biologically-active form by the host/prey, or when toxins from plant residues persist in the soil (Groot & Dicke, 2002).

3.2.2. Indirect Impacts: Since the introduction of GM crops to the market in 1996, there has been an in-

creasing interest on how changes in agriculture practices might indirectly affect the environment (Dale *et al.*, 2002). The discussions on GM pest resistant crops in many parts of the world has led to questions about their potential impacts on biodiversity through tri-trophic interactions, particularly on their effects on non-target organisms, including insect herbivores and natural enemies, as well as soil microbiota. Further concern arises from the possibility of resistance development in insect pests, which could endanger important natural resources such as the bacterium B. thuringiensis, a natural microbial insecticide. Guidelines have been developed on how to assess the wider indirect impacts of a GM crop (ACRE, 2001). They require a comparison between the management of the GM crop and the equivalent non-GM crop, with an assessment of the potential impact on key indicator species typical of arable farmland, and examples of impact mitigation are already beginning to appear (Pidgeon *et al.*, 2007).

3.3. Human and Animal Health Issues:

With regard to investigating the safety of GM foods, the key question is whether changes other than the intended new trait have occurred in the new crop (ILSI Task Force, 2004), and are typically identified from comparisons with the conventional counterpart (OECD, 2000 and FAO/WHO, 2007). Compositional parameters are selected that are typical for the crop that is assessed, and that are representative of the main metabolic pathways. Signi?cant changes in these parameters are expected to be indicative of more fundamental changes in the crop that need to be evaluated for their potential to have adverse consequence to human health (König *et al.*, 2004). However, as the degree of modification introduced by GM technology increases, at a practical level, the choice of comparators, and the range of differences encountered may make this approach more difficult to apply. Presently, while the parameters to be measured have not been formally defined, minimal analyses determine whether the major nutritional components (i.e., lipids, carbohydrates, proteins, vitamins, minerals, trace elements) and known anti-nutrients and toxins of transgenic plants are equivalent to those in conventional varieties. For livestock nutrition, important measurements include crude protein, fat, fibre, starch, amino acids, fatty acids, ash and sugar (Aumaitre *et al.*, 2002). Some of these factors not only affect animal health and performance, but can also alter the composition and quality of animal products provided to the consumer.

In the evaluation of the nutritional aspects of the GM event, the raw agricultural commodities and, on a case-by-case basis, the processed fractions are assessed for key nutrients as well as naturally occurring anti-nutrients, toxicants and secondary plant metabolites (EFSA, 2004). If compositional equivalence, except for the introduced traits, is established between a GM food or feed with its non-GM counterpart, then nutritional equivalence can be assumed (Clark & Ipharraguerre, 2001). Further nutritional analysis, including animal performance, feed and digestion studies, need only be undertaken should concerns remain (Kuiper *et al.*, 2001). Livestock feed safety is also determined, in order to ensure that unsafe residues are not introduced into human food products via the ingestion of GM feed by food-producing animals. Adverse effects of a plant fed to livestock would be a clear warning for human use.

To date, given that there are no reports of DNA itself being toxic or allergenic, and the very long human history of DNA consumption from a wide variety of sources, it is concluded that such consumption poses no significant risk to human health, and that additional ingestion of recombinant DNA, which is chemically indistinguishable from non-modified DNA, has no effect (Royal Society, 2002; Van den Eede, 2004 and FAO/WHO, 2007). Another concern regarding transgenic plant DNA that has been raised is the possible transfer of antibiotic-resistance markers (ARMs) to bacteria. However, the ARMs used in currently registered GM plants are unlikely to result in the development of resistance to the therapeutic antibiotics presently used in animal and human health (FAO/WHO, 2007). This conclusion was based on: the low probability of gene transfer from plants to bacteria; the fact that the antibiotics used as markers are rarely used in human and veterinary medicine; or are those to which widespread resistance is already prevalent in nature (EFSA, 2007). This is further supported by recent reviews that have shown that ARMs in GM plants do not pose a significant threat to human health (Bennett *et al.*, 2004; Gay & Gillespie, 2005; Goldstein *et al.*, 2005 and Ramessar *et al.*, 2007) .

4. Conclusion

In this paper the risk assessment of GM crops is discussed, in order to provide an introduction to the complexity of the subject. Although there is a broad worldwide consensus on the types of information upon which an RA is built, there is considerable national and regional variation in emphasis, and in the depth of information required by the competent authority. It is worth emphasising that the role of an effective RA is not to completely understand a natural phenomenon, but to focus on the data necessary to make a sound judgement. Superfluous data often confuses decision-making, diverting time and efforts from the more serious of the identified potential risks, thereby slowing down the procedure and increasing associated costs (Raybould & Cooper, 2005 and Andow & Zwahlen, 2006). In this regard, structuring the RA process using decision trees and/or tiered approaches should be seriously considered as a tool for focusing on the essential issues.

The status of science in national biosafety regulatory frameworks, the drafting of regulations sufficiently stringent in order to protect against genuine ascertainable risks (as determined by the application of best available science), as well as the ability of decision-makers to discern the appropriateness of data necessary to adequately conduct a risk assessment, all have considerable consequences. For exam-

ple, the critical role of science in evaluating the presence of health and environmental risks prior to the adoption of national food safety regulations, especially those not based on relevant international standards, was recently addressed in the decision of the World Trade Organization (WTO) Dispute Resolution Panel in the long-standing dispute brought by Argentina, Canada and the United States against Europe over the regulation of GM food and seed (WTO, 2006). The Panel focused on the type of evidence that a WTO member government is permitted to rely on as justification for the imposition of national/regional health and environmental regulatory restrictions that have a substantial impact on international trade flows. It judged to be inappropriate both reports by non-expert civil society (e.g. non-governmental organisations) and general scientific studies appearing in peer-reviewed journals that did not provide an assessment of specific context-based health or environmental risks according to specifically defined scientific protocols. Indeed, in the Panel's view, these sources did not constitute adequate RA because they did not take into account risk assessment techniques developed by the relevant international organizations (Kogan, 2007). In essence, the WTO Panel is proposing that decisions regarding GMOs be narrowly focused on the RA, disallowing other types of concerns. This position is at odds with those competent authorities currently attempting to incorporate socio-economic elements into their decision-making process.

Many countries (and regions) have, or are currently putting into place, a framework for undertaking RAs of the cultivation or production of GM foods, and as such, this represents a significant opportunity to work towards international harmonisation on many levels. In the authors view, this should be whole-heartedly supported by all stakeholders.

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مدخل إلى تقييم سلامة/مخاطر المحاصيل المحوَّرة وراثياً [1]

ويندي كريج [2] ومارك تيبفر [3]

الخلاصة

يُعتبر استخدام التقانات الحيوية الحديثة لاستنباط محاصيل مُحوَّرة وراثياً ثورةً حقيقية في مجال تربية النباتات، والتي تحتاجُ إلى تقييمٍ دقيق قبل الاستخدام التُّجاري. وهنالك إجماعٌ عالميٌ على أنَّ التقييم يجب أن يرتكز على ضرورة الأخذ بالاعتبار المخاطر والسلامة للمحاصيل المحوَّرة وراثياً. تتناول المقالة تقدير المخاطر ودورها في عملية صناعة القرار، كما تقوم بتوصيف مجالات الاهتمام للجيل الحالي من المحاصيل المُحوَّرة وراثياً.

1. بدأ غالبية المهتمين مؤخراً يشيرون إلى تقدير المخاطر للمحاصيل المحورة وراثياً تقديراً للسلامة بصفةٍ عامة، وذلك لتحاشي الآثار السلبية التي يفهمها الناس من كلمة مخاطر. رغم ذلك، فإنَّ هذا التعبير يحتاجُ إلى تعريفٍ دقيق وتبنٍّي واسع.

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