

Assessing environmental releases of genetically modified organisms: policy considerations of benefits and risks

Overview

- Genetically modified organisms (GMOs) hold enormous potential to improve human and environmental health, yet may also entail potential risks.
- GMO regulation in the European Union, as in most countries, occurs solely via a risk analysis, with no consideration given to benefits of the proposed technology, nor to the relative risks of competing technologies. Thus, decision-making is not contextualised & suffers from inconsistencies and ambiguities.
- A more robust approach to GMO regulation requires balancing benefits against risks via a risk-benefit analysis (RBA).
- Several regulatory approaches based on RBA are used to evaluate both GM and non-GM technologies worldwide. These can serve as precedents and parallels to guide the integration of RBA for GMO regulation.
- Avenues forward include enabling comparisons of relative risks, regulating products not processes, and regulating systems not technologies.
- A legislative framework for GMO regulation based on RBA would provide a balanced, transparent and consistent approach to decision-making.



Background

Recent advances in biotechnology have produced a collection of genetically modified organisms (GMOs) specifically engineered to exhibit traits that are beneficial to human health, food production and the environment (see Box 1). Despite the potential value of these benefits to society, numerous concerns have been raised regarding the potential risks that releases of GMOs pose for human health and the environment¹. In light of these concerns, governments and agencies wishing to benefit from GM technologies must formulate robust policies to manage any identified risks (real, or perceived) involved in their use.

To maximise net social benefit, the decision to accept or reject a particular GMO should be based on an assessment of whether the benefits outweigh the risks, given a predefined level of acceptable risk. Most countries worldwide, however, employ a regulatory framework for GMOs that focuses exclusively on risks, and does not accommodate any consideration of benefits². Moreover, most countries also explicitly mandate that these risks be assessed in isolation from the risks of competing technologies. This restricted view of risk-assessment leads to decision-making that is not contextualised and assumes that the safety evaluation of the GMO is the only decision to be made³.

A more robust, balanced approach to GMO regulation requires a legislative move away from a risk-focused framework, to a framework in which regulators assess the

degree to which a new technology improves or detracts from the delivery of wider health, environmental, social, and economic targets. In the last decade, numerous experts have called on governments to change their regulatory frameworks for GMOs, warning that adherence to the status quo will deprive society of the anticipated benefits of new technologies^{2,4,5}.

Purpose and Scope of this Report

This report aims to raise awareness of the need to consider benefits alongside risks in the regulation of environmental releases of GMOs (where release of the product involves benefits and risks to public health and the environment). It draws attention to the inadequacies of current risk-based GMO regulations, and presents some avenues for the development of more effective regulatory frameworks based on risk-benefit analysis (RBA; see Box 2). In particular, this document highlights existing RBA frameworks used to evaluate GM and non-GM technologies, which can serve as legislative precedents and parallels to guide the integration of RBA for GMO regulation. The focus throughout is specifically on GMO regulations within the European Union (EU) because, by its own admission, the EU has adopted the most stringent and restrictive GMO regulations in the world⁶. As such, this report is primarily aimed at EU agencies tasked with regulating GMOs. Nevertheless, the information and recommendations presented are applicable beyond the European setting, and it is envisaged that this report will be of interest to regulators in many agencies worldwide.

Regulation of GMOs within the EU

EU procedures for the evaluation and authorisation of environmental releases of GMOs are detailed in the Deliberate Release Directive 2001/18/EC. Authorisation of GMOs is undertaken by the European Commission (EC) on the basis of independent expert advice provided by the European Food Safety Authority (EFSA). However, even after authorisation is granted, a 'safeguard clause' provides a mechanism for EU member states to override EC decisions and ban GMO products within their territories.

The EU is a signatory of the Cartagena Protocol on Biosafety, which prescribes a precautionary approach to GM regulation dictated by a strong interpretation of the precautionary principle (Box 3)⁷⁻⁹. Indeed, a precautionary approach is a fundamental principle in EU law. The strong version of the precautionary principle has received extensive criticism and can lead to paradoxical outcomes when applied (Box 3). Despite this, EU decisions on GMOs remain guided by strict compliance with this overarching philosophy. Consequently, EU legislation states that the decision to authorise GMOs be undertaken solely on the basis of an assessment of the risks to human and animal health and the environment. Risk assessments are carried out by applicants, with EFSA providing its opinion on the applications to the EC. Importantly, EU legislation prohibits applicants from providing information on the benefits of the technology. Thus, EFSA regulators are not able to evaluate potential risks in context and may not even be aware of the potential value of a new product. EU legislation also prevents regulators from assessing the risks of GMOs in relation to the risks of alternative proposals or existing technology (other than the non-modified organism from which the novel product is derived).

This narrow approach to GM regulation arises because in the EU the status quo is considered safe and/or acceptable and because of all modern breeding methods only genetic modification is considered intrinsically 'risk-generating'. Hence, under EU legislation risk assessments are initiated not as a result of the traits of proposed products, but as a consequence of the method by which products were developed. This position has been criticised by experts, and is not supported by scientific findings^{5,10,11}. For example, studies have shown that the environmental impact of changes in agricultural management of non-GM crops can be at least as significant as those associated with GM crops¹⁰. Moreover genetic strategies for insect pest control (e.g. 'genetically sterile' insect technologies¹²) could alleviate many hazards associated with existing pest control methods (e.g. use of insecticides or extensive administration of drugs; Box 1¹³).

When the current technology is presumed safe/acceptable then it is likely that any new proposed technological change will create some risk. Even if that risk is small, a justification will be required for accepting or rejecting the risk. That justification, however, can only reasonably be made in light of the benefits of the proposed new technology. Hence, the risk-only framework for assessment of GMOs adopted in the EU creates a system in which it is extremely difficult to reach decisions that support the release of GMOs (even for GMOs that entail negligible increases in risk)¹⁴.

Box 1. Potential Benefits of GMOs

GM agricultural initiatives are engineered to provide a range of varied benefits to human health, agricultural productivity, and environmental sustainability, including:

- development of allergen-free foods and foods with greatly improved nutritional value;
- increased yields and greater profitability derived from more productive crops, and crops with improved resistance to stressors (pests, pathogens, herbicides, severe weather);
- decreased use of persistent, broad spectrum pesticides which may contaminate groundwater and affect non-target organisms;
- reduced land conversion and the possibility of rehabilitating damaged and less-fertile land (via stress-tolerant varieties and organisms that restore nutrients and soil structure).

GM insect strategies for controlling pests and insect-borne diseases offer several benefits over existing control methods, including:

- targeting single species, leaving beneficial insects unharmed;
- reducing the need for insecticides and alleviating the need for extensive use of drugs and prolonged investment in vaccine development to combat disease;
- capitalising on insects' mate-seeking abilities to potentially eliminate populations that are inaccessible, or resistant, to traditional control;
- protection for all people, irrespective of socioeconomic status;
- requiring less community involvement, facilitating the success of control programmes.

GM recombinant vaccines for the prevention of infectious diseases offer several benefits beyond those of standard vaccines including:

- extending the range of diseases which respond to vaccines;
- producing a more targeted immune response via isolation of specific proteins;
- protecting recipients from reactions to foreign antigens;
- not requiring adjuvants, which can have serious side-effects.

Box 2. Risk Analysis versus Risk-Benefit Analysis

Risk Analysis (RA)

- RA involves systematically reviewing scientific data in order to formally evaluate risks associated with certain hazards.
- A risk assessment involves (i) identifying potential hazards, (ii) evaluating the likelihood of hazards occurring, (iii) determining the potential exposure to hazards in the environment, and (iv) assessing the magnitude of an effect given exposure.
- In terms of EU GM regulations, a risk assessment is based on the characteristics of the organism, the introduced trait, the environment into which the organism is introduced, the interaction between these, and the intended application.
- Importantly, if risks are identified, then risk management and risk communication also form part of the RA.

Risk-Benefit Analysis (RBA)

- RBA encompasses an explicit assessment of both the adverse and beneficial effects of a technology, accompanied by risk/benefit management and communication.
- A risk-benefit assessment involves determining the probabilities of risks and benefits occurring given the introduction/release of the new technology. Benefits may include positive health effects, reductions of adverse health effects, a reduction of environmental risk, or a designed environmental advantage. A risk-benefit assessment does not mask risks, or minimise their importance.
- RBA proceeds by comparing the balance of risks and benefits of a particular technology with that of other viable alternatives (including the "no action" or status quo alternatives). The outcome with the best risk-benefit ratio is selected.

GMO Precedents

Several countries have adopted regulatory frameworks for GMO assessment that accommodate consideration of the benefits of the proposed technology and a comparison of relative risks among competing technologies. These existing legislative frameworks represent examples of more balanced approaches to the regulation of GMOs.

USA: The Coordinated Framework for the Regulation of Biotechnology was established in 1986 to regulate GMOs within the USA. The framework states that a commercial product, regardless of its manner of production, should be regulated based on the product's composition, its intended use, and the environment into which it would be released¹³. Hence, US policy assumes that the process of

biotechnology itself poses no unique risks¹⁵. The consideration of potential benefits alongside risks varies from explicit to implicit among different regulatory agencies. For example, FIFRA (Federal Insecticide, Fungicide and Rodenticide Act) requires the explicit consideration of both environmental risks and benefits. APHIS (Animal and Plant Health Inspection Service) though, treats potential benefits implicitly, requiring a standard risk-assessment, but making provisions to deny permits where "potential risks, despite safeguards, outweigh the potential benefits of a product"¹⁶.

Canada: Canada considers the novelty of a biotechnology product as the trigger for regulatory review, rather than the particular method by which the product was developed¹⁷. The application of genetic modification via traditional breeding or genetic engineering is not considered to alter the inherent risk associated with a particular product. Hence, like the US, Canada regulates the product rather than the process.

New Zealand: New Zealand's Environmental Protection Authority regulates the release of GMOs under the Hazardous Substances and New Organisms Act 1996 and the Biosecurity Act 1993. Regulators must identify, assess, and evaluate the balance of both the adverse and beneficial effects of the proposed technology¹⁸. Applications are only approved if the benefits outweigh the risks. New Zealand's directive to consider benefits alongside risks offers an important precedent for GMO regulation.

Non-GMO Parallels

Risk-benefit assessments are regularly undertaken in Europe and abroad in a wide range of disciplines concerned with evaluating novel non-GM technologies. These regulatory frameworks serve as legislative parallels that can inspire and guide the integration of risk-benefit assessment for regulation of GMOs.

European Commission's Impact Assessment Guidelines

In 2009, the European Commission published a guidance document for undertaking impact assessments that aimed to improve the quality of policy proposals by providing transparency on the benefits and costs of different policy alternatives. The guidelines stress that the positive and negative impacts for each option must be weighed-up on the basis of criteria that are clearly linked to objectives²¹.

EFSA's RBA of Foods for Human Health

A guidance document prepared by EFSA's Scientific Committee in 2010 states that "where a food or food

Box 3. Criticisms of use of the Strong Version of the Precautionary Principle (PP)

The PP enables regulators to make discretionary decisions in situations where an action or proposal entails the possibility of harm to the environment (including human, animal and plant health) and when extensive scientific knowledge on the matter is lacking. Several different definitions of the PP exist. The EU's regulation of GMOs adheres to a strong version of the PP prescribed within the Cartagena Protocol:

Lack of scientific certainty due to insufficient information... shall not prevent the Party of import, so as to avoid or minimize such potential adverse effects, from taking a decision... regarding the import of the living modified organisms.

Use of the strong PP has been criticised on several grounds.

- It can be over-interpreted to imply that something should not be done if it is risky. In regulatory terms, this is analogous to comparing a GMO to a risk-free (non-existent) ideal alternative.
- Direct application of the strong version of the PP can lead to paradoxical outcomes⁹. Precautionary measures taken to avoid harm, might themselves involve a risk of harm. E.g. enforcing carbon emission reductions could cause substantial social and economic upheaval. Alternatively, precautionary measures might cause harm if they prevent a 'good effect' from occurring, e.g. by depriving society of a benefit of a proposed technology.
- Application of the PP has been criticised for being arbitrary, ambiguous and subject to political whim. E.g. within the EU, the PP is applied to GM crops, but not to non-GM crops with similar features. It is applied to GM foods, but not to dietary supplements, which may also have health risks. Likewise, the PP is not applied to regulate lucrative activities like tourism, despite their potential to cause environmental damage.
- A strong interpretation of the PP could be used to restrict trade or to protect domestic agriculture. In its adoption of the PP in this manner, the EU has been criticised for allowing economic protectionism to masquerade as environmental protection¹⁹.
- The EU's strict adherence to the strong version of the PP to regulate GMOs contradicts the European Commission's statement on the use of the PP. This statement declares that use of the PP should be guided by the "principles of proportionality, non-discrimination and consistency, and include an examination of the risks and benefits of action and inaction"²⁰.

substance is recognised to have the potential to exert both health benefits and health risks it is important for regulators to be able to weigh the risks against the benefits on the basis of a qualitative or quantitative risk-benefit assessment"²². This recognises that regulatory measures taken solely from a risk point of view could restrict the availability of a given food, and that the health consequences of not eating that food might be more serious than the risk. This approach to regulation is diametrically opposed to EFSA's position on the regulation of GMOs. A recent study found that this proposed risk-benefit assessment framework for foods could be readily integrated into current GMO assessment policies, and would improve transparency and confidence in the GMO regulatory process⁴.

Australia's RA on the release of *Wolbachia* mosquitoes

In 2010, Australia's CSIRO laboratories undertook an independent risk analysis of a proposed release of mosquitoes infected with *Wolbachia*, a maternally-inherited intracellular bacterium, to control dengue virus²³. Infection

with *Wolbachia* is deemed a non-transgenic modification, and is not regulated by restrictive GMO regulations¹⁹. Instead, a bespoke risk analysis was conducted adopting a comparative risks paradigm - i.e. the analysis assessed the risk that the proposed release would "cause more harm" than that expected to be caused by naturally occurring mosquitoes and dengue virus (e.g. "cause more disease"²³). Importantly, no change (e.g. no more disease) was sufficient for approval. This approach recognises the inherent risks of not taking action, and implies there was an acceptable level of risk that could be tolerated²⁴.

Australia's Regulation of Biological Control Measures

Australia's Biological Control Act provides the regulatory framework for evaluating the safety and efficacy of the release of live organisms to control pest species. Regulators must undertake a full RBA including an assessment of the economic and environmental losses caused by the target, and the benefits of its control²⁵. It is the regulator's duty to weigh the risks, benefits, and costs of a release against the risks, benefits, and costs of alternative pest control options. Similar bio-control acts exist in New Zealand and Canada.

Regulation of Medicines and Healthcare Products

Balancing the desirable (benefits) and undesirable effects (risks) of drugs, vaccines (including GM vaccines) and medical equipment is the core task of healthcare regulatory agencies. The UK's Medicines and Healthcare products Regulatory Agency (MHRA) stipulates that new medical products are approved only if evidence shows that the potential benefits will outweigh the likely risks²⁶. The MHRA notes that no product is risk-free, and that greater risks may be acceptable for products that provide greater benefits, particularly if no other effective treatment is available. They also advise that patients are usually free to choose to use a product or not, based on information about its potential benefits and side-effects (risks).

Avenues for Integrating RBA in GMO Regulation

Introduce a Comparative Risks Approach to RA

An initial measure to introduce a more balanced regulation of GMOs within the EU (and elsewhere) is to assess the risks of a GMO against those of existing and alternative technologies. In this approach, benefits are not explicitly characterised but instead are implicitly considered in terms of understanding and identifying the relative risks of competing technologies.

Regulate the Product not the Process

As discussed above, the EU's current regulatory framework for GMOs is process-based. Products produced by GM methods receive strict risk assessments, whereas products whose genetic constitution has been modified by other breeding techniques (e.g. by radiation) do not. Aside from assuming that non-GM technologies are completely safe, this approach contradicts the European Commission's directive that the PP be applied to new technologies "consistently and regardless of the nature of the production process"²⁰. In addition, under this regulatory approach it is possible for two identical novel products to be regulated differently. For example, mutagenesis is a non-GM technique capable of producing products that are genetically identical to those produced by GM techniques²⁷. Such inconsistencies will increase as new biotechnologies emerge that similarly fall

outside the definitions of current process-based legislation⁷. Consequently, a more robust regulatory framework should focus on assessing the risks and benefits of novel products, rather than products produced by particular technologies.

Regulate Systems rather than Technologies

Environmental releases of GM technologies are often designed to be implemented as integrated systems, with a suite of accompanying activities undertaken alongside the release of the GM product. For example, GM insect pest control strategies involve rearing and releasing insects, training personnel, and extensive monitoring and managing of target objectives. Similarly, GM crops are expected to be implemented alongside agricultural management activities that enhance yield and minimise impacts (e.g. crop configuration, tillage practices, resistance management). In many situations then, the efficacy of a proposed GM release will be intimately linked to the complementary actions undertaken to support it. Hence, assessment of GMOs should explicitly consider proposed systems as a whole. The value of assessing whole systems is seen in the contrasting outcomes of the long-term use of herbicide resistant GM crops (HR crops) and insect resistant GM crops (IR crops) in the US²⁸. HR crops (e.g. those resistant to glyphosate) were approved and implemented without a mandatory requirement to undertake supplementary management practices. Today these products are plagued by problems with field resistance and the spread of HR weeds. In contrast, evolved field resistance has been far less problematic for the efficacy of IR crops (e.g. those expressing *Bacillus thuringiensis* toxin), which were approved and implemented with a mandatory requirement for stringent resistance management practices^{28,29}.

Best practices for implementing RBA

- RBAs should be evidence based and include consideration of reasoning, assumptions and uncertainties. This will be crucial for qualitative and semi-quantitative RBA analyses.
- RBAs should be undertaken case-by-case, drawing on existing information and knowledge gained from previous experience.
- Risks and benefits must be treated in the same way in a RBA. EFSA's guidance document for RBA of foods for human health concluded that a RBA should mirror the RA approach (Box 2)²².
- Hence, a RBA should: (i) identify both hazards and positive effects; (ii) assess the likelihood of the hazards/positive effects occurring; (iii) assess the magnitude of effects given their occurrence; and (iv) characterise risks and benefits in terms of the combined likelihood and magnitude of effects³.
- RBA will require a method to objectively weigh risks against benefits on a common scale²².

Conclusions

In Europe, and elsewhere, a more balanced and consistent approach to the regulation of GMOs and new technologies is needed. As this report argues, adopting a RBA framework for assessing and regulating competing technologies is widely regarded as providing the most balanced, transparent, robust, and comprehensive approach to social decision-making^{14,30}. A legislative shift to RBA for GMO regulation would also conform to the principles of proportionality, nondiscrimination and consistency, and ensure that regulatory frameworks are as simple and effective as possible.

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References

1. Torgersen, H. (2004) The real and perceived risks of genetically modified organisms. *EMBO Rep.* 5, S17-S21, <http://dx.doi.org/10.1038/sj.embor.7400231>.
2. MacDonald, P. (2012) Developing workable regulatory frameworks for the environmental release of transgenic plants. *International Centre for Genetic Engineering and Biotechnology: Collection of Biosafety Reviews* 6, 126-159 http://www.icgeb.org/~bsafesrv/pdf/files/Col6_Macdonald.pdf
3. Morris, E.J. (2011) A semi-quantitative approach to GMO risk-benefit analysis. *Transgenic Research* 20, 1055-1071. <http://dx.doi.org/10.1007/s11248-010-9480-8>
4. Kuiper, H. A. & Davies, H. V. (2010) The Safe Foods Risk Analysis Framework suitable for GMOs? A case study. *Food Control* 21, 1662-1676. <http://dx.doi.org/10.1016/j.foodcont.2010.02.011>.
5. Drobnik, J. (2008) Time to relax GMO regulation in Europe. *Plant Cell Tissue Organ Cult.* 94, 235-238, <http://dx.doi.org/10.1007/s11240-007-9331-3>.
6. European Commission. (2005) Environment fact sheet: genetically modified organisms: [http://www.envirocentre.ie/includes/documents/genetically%20modified%20organisms%20\[1\].pdf](http://www.envirocentre.ie/includes/documents/genetically%20modified%20organisms%20[1].pdf)
7. Morris, S. H. & Spillane, c. (2008) GM directive deficiencies in the EU: The current framework for regulating GM crops in the EU weakens the precautionary principle as a policy tool. *EMBO Rep.* 9, 500-504. <http://dx.doi.org/10.1038/embor.2008.94>
8. Marchant, G. E. & Mossman, K. L. (2004) Arbitrary and Capricious: The Precautionary Principle in the European Union Courts. *Union Courts*.
9. Clarke, S. (2009) *in* Evaluating New Technologies (eds P. Sollie & M. Duwell) pp. 159-174 Springer.
10. UK Advisory Committee on Releases to the Environment. (2007) Managing the footprint of agriculture: towards a comparative assessment of risks and benefits for novel agricultural systems. <http://goo.gl/vjbzn>
11. Masip, G. Et al. (2013) Paradoxical EU agricultural policies on genetically engineered crops. *Trends in Plant Science*. <http://dx.doi.org/10.1016/j.tplants.2013.03.004>
12. Morrison, N. I. & Alphey, L. (2012) Genetically modified insects for pest control: an update. *Outlooks Pest Management* 23, 65-68. <http://dx.doi.org/10.1564/23apr05>
13. Pew Initiative on Food and Biotechnology. (2004) Bugs in the System? Issues in the science and regulation of genetically modified insects. Pew Initiative on Food and Biotechnology, Washington. http://www.pewtrusts.org/our_work_report_detail.aspx?id=17984
14. Linacre, N., Falck-Zepeda, J., Komen, J. & MacLaren, D. (2006) Risk assessment and management of genetically modified organisms under Australia's gene technology act. International Food Policy Research Institute, Environment and Production Technology Division, Washington D.C. <http://goo.gl/5mwvi>
15. Committee on Genetically Modified Pest-Protected Plants National Research Council. (2000) *in* Genetically Modified Pest Protected Plants: Science and Regulation. National Research Council USA. pp. 5-6. Academy Press. http://www.nap.edu/openbook.php?record_id=9795&page=R21
16. Department of Animal and Plant Health Inspection Service. (2011) Code of Federal Regulations. pp. 483-490 US Government Printing Office, Washington D.C., USA.
17. Canadian Food Inspection Agency. Regulating agricultural biotechnology in Canada: an overview, <http://www.inspection.gc.ca/plants/plants-with-novel-traits/general-public/factsheets/overview/eng/1338187581090/1338188593891> (2012).
18. NZ Environmental Protection Authority. (2011) A technical guide to identifying, assessing and evaluating risks, costs and benefits. New Zealand Government. <http://goo.gl/7wxCK>
19. Marshall, J. M. (2011) The Cartagena Protocol in the context of recent releases of transgenic and *Wolbachia*-infected mosquitoes. *Asia Pacific Journal of Molecular Biology and Biotechnology*. 19, 93-100. <http://www.msmbb.org.my/apjmbb/html193/193c.pdf>
20. European Commission, Brussels (2000) Communication from the Commission on the precautionary principle. http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf
21. European Commission. (2009) Impact assessment guidelines. European Commission. http://ec.europa.eu/governance/impact/commission_guidelines/commission_guidelines_en.htm
22. EFSA Scientific Committee. (2010) Guidance on human health risk-benefit assessment of food. *EFSA Journal* 8, 1-44. <http://www.efsa.europa.eu/en/scdocs/doc/1673.pdf>
23. Murphy, B., Jansen, C., Murray, J. & De Barro, P (2010) Risk Analysis on the Australian release of *Aedes aegypti* containing *Wolbachia*. Commonwealth Scientific and Industrial Research Organisation, Brisbane, Australia. <http://goo.gl/x5Wlr>
24. Mumford, J. D. Science, Regulation, and Precedent for Genetically Modified Insects. *PLoS Negl Trop Dis* 6, e1504, <http://dx.doi.org/10.1371/journal.pntd.0001504> (2012).
25. Australian Government. Biological Control Act (1984) No. 139 of 1984. Office of Legislative Drafting and Publishing, Canberra. <http://www.comlaw.gov.au/Details/C2008C00315>
26. Medicines and Healthcare products Regulatory Agency. (2007) Making regulatory decisions about medicines and medical devices. Medicines and Healthcare products Regulatory Agency, UK. <http://goo.gl/Twu8u>
27. Oh, T. J. & May, G. D. (2001) Oligonucleotide-directed plant gene targeting - Commentary. *Current Opinions in Biotechnology*. 12, 169-172, [http://dx.doi.org/10.1016/s0958-1669\(00\)00194-4](http://dx.doi.org/10.1016/s0958-1669(00)00194-4).
28. Frisvold, G. B. & Reeves, J. M. (2010) Resistance management and sustainable use of agricultural biotechnology. *Journal of Agrobiotechnology Management and Economics* 13, 343-359. <http://www.agbioforum.org/v13n4/v13n4a07-frisvold.htm>
29. Tabashnik, B. E., Gassmann, A. J., Crowder, D. W. & Carriere, Y. (2008) Insect resistance to Bt crops: evidence versus theory. *Nature Biotechnology* 26, 199-202. <http://dx.doi.org/10.1038/nbt1382>.
30. de Melo-Martin, I. & Meghani, Z. (2008) Beyond risk: a more realistic risk-benefit analysis of agricultural biotechnologies. *EMBO Rep.* 9, 302-306, <http://dx.doi.org/10.1038/embor.2008.39>.