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# Putting problem formulation at the forefront of GMO risk analysis

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**W**hen applying risk assessment and the broader process of risk analysis to decisions regarding the dissemination of genetically modified organisms (GMOs), the process has a tendency to become remarkably complex. Further, as greater numbers of countries consider authorising the large-scale dissemination of GMOs, and as GMOs with more complex traits reach late stages of development, there has been increasing concern about the burden posed by the complexity of risk analysis. We present here an improved approach for GMO risk analysis that gives a central role to problem formulation. Further, the risk analysis strategy has been clarified and simplified in order to make rigorously scientific risk assessment and risk analysis more broadly accessible to diverse stakeholder groups.

## The Challenge of Improved Risk Analysis for Deliberate Release of GMOs

There has been growing concern over the burden posed by the complexity of the risk analysis process being applied to GMOs,<sup>1</sup> especially in countries relatively new to authorizing large-scale GMO dissemination, but also since GMOs with more complex traits are now reaching the later stages of development. As part of its capacity building activities, the International Centre for Genetic Engineering and Biotechnology (ICGEB) has devoted several week-long training courses to applying a stepwise approach based on problem formulation to link the policy objectives that drive risk analysis to the assessment of the potential impact(s) of the large-scale

unconfined release of specific GMOs. This approach, which we present here, is the result of incremental developments and improvements based upon participant feedback over a series of focused training workshops (see supplemental materials), and therefore has several novel features compared with previous strategies that also center on problem formulation: the initial step is open to consideration of all types of concerns, including socio-economic impacts; an additional prioritisation step facilitates dealing rapidly with certain potential risks; and avoidance of specialist vocabulary makes the process more accessible to non-experts.

The ICGEB began offering annual week-long training courses in biosafety in 1991. Since 2009, it has provided practical training in an approach based on problem formulation, in order to link the policy objectives that drive risk analysis to the assessment of the potential impact(s) of the dissemination of specific GMOs (see Supplemental Materials). In our experience, the approach developed through the courses is particularly useful for clarifying the exact nature of potential risks: determining what organisms or other features we don't want to be harmed, how they could be harmed, how likely they would be harmed, and whether it matters if they were.<sup>2</sup> This approach also helps distinguish those data that are essential for risk assessment from those that would merely explain scientific phenomena but that may be nice to know from the perspective of familiarity.

In order to be as concrete as possible, the courses were built largely around hypothetical—but plausible—case studies. The case studies were presented only

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- (1) Identify policy objectives
  - Protect environment, human and animal health
  - Social and economic goals
- (2) Based on these objectives, create a list of undesirable harms
- (3) Reformulate the harms as a catalogue of risk hypotheses
- (4) Prioritisation: rank the hypotheses according to their importance, and deal quickly with those with small impact
- (5) For the hypotheses to be examined in greater detail, create a pathway to harm
- (6) Test the risk hypotheses
  - Identify key steps in the pathway, and add available data where pertinent
  - Determine if the existing data break the causal chain of events in the pathway to harm
  - If not, identify what additional data would allow satisfactory testing of the hypothesis
- (7) If concerns remain, consider mitigation measures that could apply
- (8) Risk assessment

**Figure 1.** Steps in the risk analysis strategy used at ICGEB training courses in risk analysis for the unconfined release of GMOs.

briefly, with simple outlines of pertinent data, since the objective was not to carry out a risk assessment, but rather to learn to apply the problem formulation strategy we developed, and within the time frame of the workshops it was impossible to present complete sets of real data concerning the case studies. We will use examples from the workshops, but they should be considered just as illustrations of the risk assessment strategy.

### **Integrating Problem Formulation in the Process of Risk Analysis**

When faced with a complex decision-making situation in any field, reformulating the issues as a series of individual problem statements can render decision-making more tractable.<sup>3</sup> The steps for integrating problem formulation in a GMO risk analysis that we have used in training courses are shown in **Figure 1**, and as will be seen below, they differ from the steps and their manner of formulation from other recently published examples,<sup>4-7</sup> which guide risk assessment specifically for addressing environmental harms. The range of harms proposed by ICGEB trainees have consistently not been limited to those occurring to the environment (**Table 1**), and compared with other strategies more importance has been given to

the elaboration of the various pathways to harm and an evaluation of where present knowledge fits on the pathways. We have found this explicit development of the problem formulation strategy particularly useful as a tool for focusing on what is known or not, and from there to determine if any additional information would be required for making scientifically valid conclusions on the potential risks being considered. The steps presented in **Figure 1** will be described in detail below.

**Setting the stage by considering the policy objectives.** Before GMO risk assessment can begin, it is essential to understand what policy objectives the overall analysis is aiming to address, with the most obvious being mandated by national law and international treaties. Although protection of the environment and human health are universally required, consideration of animal health and also socio-economic and cultural impacts are highly contextual and hence not universally regulated, although it has been suggested that risk assessment could also be fruitfully applied to concerns in these areas related to GMOs.<sup>8,9</sup> For instance, fighting poverty is a policy objective that is particularly appropriate in certain developing countries, yet this is not mandated in many national GMO regulations. The policy objectives identified by the participants at our various workshops

were more or less the same: (1) Protecting the environment; (2) Protecting human health; (3) Protecting animal health; (4) Ensuring food security and enhancing poverty alleviation; (5) Preventing negative impact on trade; (6) Ensuring compatibility with social and cultural values. Although focusing principally on how these policy objectives may be negatively impacted by the dissemination of a particular GMO, the approach is entirely compatible with considering expected benefits in the decision-making process.

**Considering the potential harms and creation of a catalog of risk hypotheses.** The identification of potential harms is central to problem formulation, but the lack of consensus on how to value the entity potentially harmed presents serious difficulties to the GMO regulators and/or risk assessors who are ultimately left to resolve the issue. After an initial discussion of policy objectives, the workshop participants were asked to assemble a list of potential harms that could be derived from the unconfined release of the GMO in question and are attributable to the introduced genetic material. Since one of the goals of risk analysis is to address public concerns, the participants were requested to consider at the outset everything that they believe to be important; at this stage, no issue was out of bounds nor too trivial

**Table 1.** Prioritization of a selection of the risk hypotheses developed for the cultivation of drought-tolerant (DT) white maize in Kenya (Nairobi 2010 and Trieste 2012 workshops)

Risk hypothesis			
	Requiring consideration	Prioritization with small consequence	Why consequences are small
DT maize will lead to increased pest and disease populations when it is planted off-season (dry season)	X		
DT maize cultivation would lead to increased greenhouse gas emissions.		X	Growing maize contributes little to greenhouse gas production, so any conceivable increase would be minor.
Extension of DT maize hectareage will lead to loss of protected species.	X		
DT maize will decrease populations of beneficial soil organisms.	X		
DT maize would increase eutrophication of water sources due to increased biomass.		X	No significant increase of biomass expected, and little maize residue is transported to water bodies.
Increased levels of aflatoxins in DT maize will lead to increased toxicity for consumers	X		
DT maize consumption will result in increased obesity levels as a result of higher carbohydrate intake in diet.		X	Higher carbohydrate consumption is a desired effect for the poor. No increase in maize consumption among the wealthy is expected, where obesity could be a problem.
DT maize consumption will result in reduced human reproductive health.		X	The transgene-encoded proteins are already abundant in the human diet.
DT maize stems will have lower nutritional value, and thus have a negative effect on humans who chew the stems, particularly children.	X		
Supplemental irrigation allows increased cultivation of DT maize, and will lead to increased soil salinity.	X		
Consumption of drought tolerant maize will compromise antibiotic treatments.	X		
DT maize will not yield higher than conventional maize under water stress conditions, resulting in unexpected crop failure and lack of contingency planning.	X		
DT maize will compromise the production of non-GM maize and hence affect maize exports.	X		
DT maize cultivation will be extended to new areas, leading to land use conflict with pastoral communities.	X		
The adoption of DT maize cultivation will result in the reduction of genetic diversity of landraces	X		

for consideration. These harms were then restated as risk hypotheses in the form of declarative sentences that describe exactly what could be harmed and how this would occur (See Table 1 for examples from a hypothetical drought-tolerant maize case study). In our experience, because of

repetitions and overlaps, the number of risk hypotheses in the catalog is less than the initial collection of potential harms. It is important that the risk hypotheses correspond to the defined policy objectives, so that there is clear agreement on what is being protected and why. Transforming

loosely worded concerns into clearly stated testable risk hypotheses is the heart of problem formulation. And indeed this has often proved to be particularly difficult for trainees to carry out when presented with concrete case studies. Also, there has been a pronounced preference by participants

to formulate the risk hypotheses as positive statements, as opposed to attempting to refute hypotheses stated in the negative form, as previously proposed.<sup>1,6</sup> The positive form appeared to help stimulate thought processes, especially for those participants not intimately involved in scientific research. Therefore no attempts were made to force participants to use the negative form. Interestingly, some hypotheses were proposed for more than one case study, especially those concerned with impacts on biodiversity that were mediated by gene flow, impacts on farmer income due to trait failure or unintentional infringements of intellectual property rights, and impacts on human reproductive health due to consumption of GMOs in general.

**Prioritizing potential risks.** Although not previously included in formal schemes of GMO risk analysis, it is remarkably useful to examine all the possible harms and the corresponding risk hypotheses in order to rank them in terms of how they can be dealt with. As noted, from a general perspective, only a small proportion of the issues involved in a complex decision-making process may need in-depth consideration.<sup>3</sup> In the case of GMOs, it is clear that the possible harms vary greatly in their potential impact, and it is certainly appropriate to devote more time and effort to the consideration of the more serious issues. Upon inspection, many pathways to harm can be rejected from detailed consideration because one or more steps can be dismissed if proven to be non-existent or highly unlikely from existing knowledge.<sup>1,9</sup> In essence, prioritization creates a short loop for removing certain potential harms from further consideration, without going through the process of creating a detailed pathway to harm, as explained below for the remaining risk hypotheses. Table 1 highlights this process, based on a drought-tolerant maize case study.

**Creating a pathway to harm for each risk hypothesis.** The pathway to harm, sometimes referred to as a “conceptual model,”<sup>1,2,7,10</sup> or “scenario,”<sup>11</sup> is a chain of cause and effect that links the initial cause (i.e., dissemination of the GMO) with a potential harm. The pathway may be branched, and there may be alternative ways of breaking it down into specific

steps, but what is important is that each step is formulated in a way that can be evaluated in the light of data. Even before considering the data that may be pertinent to testing the risk hypothesis, careful scrutiny of the pathway to harm will identify which steps may be most decisive in attempting to break the pathway. A particularly useful feature of this stepwise analysis of the pathway to harm is that it suffices to break one step in the pathway decisively to invalidate the risk hypothesis and conclude that the likelihood that any harm will occur via that pathway is minimal.

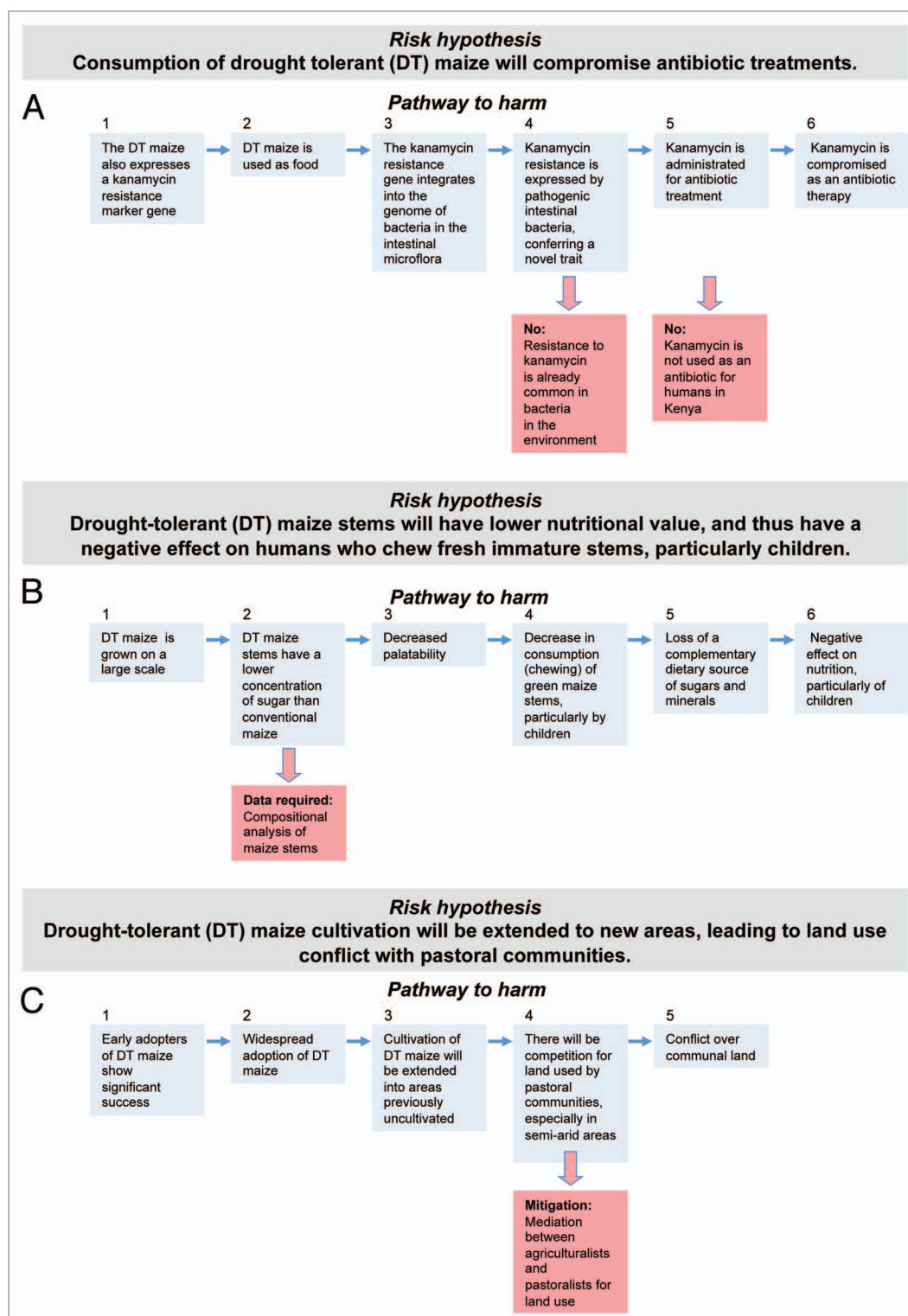
**Testing the risk hypothesis by examining the pathway to harm and the existing data.** Once the steps in the pathway have been established, they can then be subjected to scientific scrutiny, through the application of existing knowledge and data, and if necessary, the generation of new data specifically addressing the step in question. When a GMO has reached the stage of consideration for unconfined dissemination, the developer will have accumulated a vast body of data concerning not only the intended use, but also regarding the host organism, the transgenes, the environment into which the GMO is proposed to be released, and their interactions. The next step is to select from among the data provided the information relevant to attempting to break one or more steps of the pathway to harm. It should be noted that in doing this, one may find data that is pertinent to the risk hypothesis, but does not fit comfortably with a precise step in the pathway. In this case, it is worth considering modifying the manner in which the pathway to harm has been broken down into steps, in order to incorporate all data that may help test the risk hypothesis as clearly as possible. In Figure 2, we give examples of three outcomes of testing the pathways to harm. In the first case, one or more steps in the pathway are broken (Fig. 2A), in the second, the data were not sufficient to produce a decisive break, and thus the participants requested further analyses (Fig. 2B). And in the third, here again there was no clear break in the pathway, so the participants suggested that dissemination should be accompanied by specific mitigation measures (Fig. 2C).

**Examining the limits of our knowledge concerning the potential risk.** It is important to recognize that the data do not necessarily lead to a formal refutation of the risk hypothesis, but this is often the case with scientific hypotheses. The data may not show that impact is impossible, which would be a formal refutation, but that the exposure or the degree of harm is sufficiently low for the impact to be considered negligible. Nonetheless, careful evaluation of the steps in the pathway to harm often makes it possible to show if the potential impact is large or small relative to other factors external to the pathway that are already known to have an impact on the protected entity. The ability to make the distinction between major and minor factors facilitates going forward with a decision by the competent authorities regarding the proposed unconfined release.

## Conclusions and Perspectives

We have used the risk analysis strategy described here for capacity building in how to address, in a scientifically rigorous fashion, potential undesirable impacts from the unconfined release of GMOs. Since consideration of socio-economic issues is possible but not mandatory for signatory parties of the Cartagena Protocol on Biosafety, we left open to the participants whether or not they wished to also consider these issues. In our experience, this has often been helpful, providing clarity in identifying precise potential socio-economic harms, how they could occur via a pathway to harm, whether the pathways are indeed plausible, and if so, whether the harms can be mitigated without losing the advantages of the GMO. Working with participants from around the world has reinforced our belief that not only are there great differences in the degree of public concern about GMO biosafety globally, but there are also real differences in the types of concerns that are viewed as most important. For example, in developing countries, there is quite reasonable concern about the potential impact on the food security of smallholder farmers, while this is of little or no pertinence in regions of large-scale modern agriculture. Since risk analyses are performed to support





**Figure 2.** An example of how a risk hypothesis can be made explicit by developing a pathway to harm. The three examples presented are taken from a hypothetical case study of drought-tolerant maize for release in Kenya. (A) The participants concluded this to not be a significant problem, since resistance to kanamycin is already common in bacteria in the environment (breaking step 6) and kanamycin is not used as an antibiotic for humans in Kenya (breaking step 7). (B) Green maize stems are a complementary source of nutrients for small children in Kenya and elsewhere in Africa. The workshop participants considered that compositional analysis of maize stems at the stage of development where they are consumed was essential. (C) The workshop participants considered that the best solution to this potential problem would be to set up a system for mediation between agriculturalists and pastoralists regarding land use, in order to avoid conflicts over land use.

the decision-making process in response to the public's concerns, in order to do so successfully, the risk assessors and decision-makers must respond fearlessly to all the issues for which risk analysis is of use in decision-making. Avoidance of issues is likely to simply delay having to face them, and may also lead to the displacement of public concern to issues where discussion is allowed.<sup>11</sup> For instance, if the consideration of socio-economic issues is not allowed in making decisions, this may create pressure for disguising them as ecological ones, which simply makes them more difficult to address.

Socio-economic and cultural-based risk hypotheses were consistently proposed by workshop participants, indicating that even if they do not fall under a clear policy mandate, these concerns remain a key pre-occupation. This further suggests that the discriminating question regarding the usefulness of problem formulation is whether or not the potential harm can be stated as a scientific hypothesis. Although the problem formulation strategy may be useful for evaluating certain socio-economic impacts, it is probably not appropriate for resolving ethical concerns, which require a completely different set of tools. From a training perspective, the best strategy is to be pragmatic; if for certain types of concern it becomes apparent that problem formulation does not create the desired clarity, then other tools can and should be used. However, in an official risk assessment setting, the policy objectives to consider are simply those mandated by law.

Beyond the capacity-building context, our experience is that the strategy described here is also quite useful to researchers involved in GMO risk assessment at the early stages of product development, since careful scrutiny of the pathway to harm makes it possible to focus research on the key step(s) in the pathway, identifying those most amenable to invalidating the risk hypothesis. Furthermore, we believe that this strategy will also be of real use in pinpointing the state of scientific knowledge regarding the risks, thereby aiding communication between biotechnology developers and risk assessors, and more generally among the various actors in decision-making. And particularly if technical risk assessment vocabulary is replaced by

more common terms, the mechanisms of the risk analysis can be more easily explained to a non-specialist audience. This can enhance public understanding of the processes underlying risk assessment.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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#### Supplemental Materials

Supplemental materials may be found here:

<http://www.landesbioscience.com/journals/gmcrops/article/22906/>

#### References

1. Raybould A. The bucket and the searchlight: formulating and testing risk hypotheses about the weediness and invasiveness potential of transgenic crops. *Environ Biosafety Res* 2010; 9:123-33; PMID:21975253; <http://dx.doi.org/10.1051/cbr/2011101>.
2. Gray A. Problem Formulation in Environmental Risk Assessment for Genetically Modified Crops: A Practitioner's Approach. *Colln. Biosafety Rev*. 2012; 6:10-65.
3. Keeney RL. Making better decision makers. *Decis Anal* 2004; 1:193-204; <http://dx.doi.org/10.1287/deca.1040.0009>.
4. AHTEG. (2011) Guidance on risk assessment of living modified organisms (revised on 4 July 2011). Secretariat of the Convention on Biological Diversity [http://bch.cbd.int/forum/ahteg/ra\\_guidance\\_revision/ra\\_guidance\\_v4july2011.doc?download](http://bch.cbd.int/forum/ahteg/ra_guidance_revision/ra_guidance_v4july2011.doc?download)
5. EFSA. Guidance on the environmental risk assessment of genetically modified plants. *EFSA J*. 2010; 8:1879-990.
6. Hokanson KE, Ellstrand NC, Ouedraogo JT, Olweny PA, Schaal BA, Raybould AF. Biofortified sorghum in Africa: using problem formulation to inform risk assessment. *Nat Biotechnol* 2010; 28:900-3; PMID:20829822; <http://dx.doi.org/10.1038/nbt0910-900>.
7. Wolt JD, Keese P, Raybould A, Fitzpatrick JW, Burachik M, Gray A, et al. Problem formulation in the environmental risk assessment for genetically modified plants. *Transgenic Res* 2010; 19:425-36; PMID:19757133; <http://dx.doi.org/10.1007/s11248-009-9321-9>.
8. Johnson KL, Raybould AF, Hudson MD, Poppy GM. How does scientific risk assessment of GM crops fit within the wider risk analysis? *Trends Plant Sci* 2007; 12:1-5; PMID:17161972; <http://dx.doi.org/10.1016/j.tplants.2006.11.004>.
9. Meyer H. Systemic risks of genetically modified crops: The need for new approaches to risk assessment. *Environ. Sci. Europe* 2011; 23:7; <http://dx.doi.org/10.1186/2190-4715-23-7>.
10. USA EPA. (1992) Framework for Ecological Risk Assessment. EPA/630/R-92/001 Risk Assessment Forum, U.S. Environmental Protection Agency (USA EPA), Washington DC, USA. [http://rais.ornl.gov/documents/FRMWRK\\_ERA.PDF](http://rais.ornl.gov/documents/FRMWRK_ERA.PDF).
11. Schenkel R. Science policy. The challenge of feeding scientific advice into policy-making. *Science* 2010; 330:1749-51; PMID:21205654; <http://dx.doi.org/10.1126/science.1197503>.