Risk Mitigating Strategies for GM Products: will they impact on estimated risk and regulatory requirements?

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Introduction

A multitude of strategies are currently being developed to mitigate the potential health and environmental risks associated with genetically modified organisms (GMOs). These include targeted transgene integration, cisgenics, tissue-specific transgene expression, chloroplast transformation, grafting on genetically modified rootstock and microRNA induced gene silencing. To help ensure the effective deployment of these strategies within South Africa's regulatory environment we investigate under **which conditions particular risk mitigation strategies (RMS) may be beneficial to mitigating identified risks or decreasing regulatory requirements** so that sound regulatory decisions can be made while harnessing the benefits of biotechnology.

Risk assessment framework

A risk analysis for the commercial use of GMOs and their products contains a number of steps including risk assessment and risk management. Risk assessment is the process whereby possible risks to human health and the environment are identified and characterised. Risks are characterised by taking into consideration both the likelihood and consequence of plausible pathways to harms using a comparative risk assessment framework. A risk assessment matrix is a valuable tool that can be used to assist in estimating risk within such a framework (Fig. 1).

		RISK ESTIMATE			
LIKELIHOOD ASSESSMENT	Highly likely	Low	Moderate	High	High
	Likely	Low	Low	Moderate	High
	Unlikely	Negligible	Low	Moderate	Moderate
	Highly unlikely	Negligible	Negligible	Low	Moderate
		Marginal	Minor	Intermediate	Major
		CONSEQUENCE ASSESSMENT			

Figure 1. Risk assessment matrix used to estimate risk (adapted from OGTR ,2009)

In the risk matrix used above there are four estimates of risk, namely negligible, low, moderate and high. The threshold for determining what an acceptable level of risk is will generally be dependent on the risk benefit analysis which will be determined on a case by case basis. However below are three levels of risk that can be applied for the purposes of risk evaluation (adapted from OGTR, 2009).

- Risks generally considered as unacceptable except in extraordinary circumstances (expected if risk estimate is 'moderate' or 'high').
- Risks generally considered as acceptable, but may require some mitigation (expected if risk is estimated as 'low').
- Risks generally considered as broadly acceptable (expected if risk is estimated as 'negligible').

Except in extraordinary circumstances risks initially identified as 'moderate' or 'high' will require risk mitigation to bring the overall level of risk for that identified risk to 'low' or 'negligible'.

Risk management of plausible risks

Risk management is the step in risk analysis whereby mechanisms are put in place to mitigate identified risks to acceptable levels. A risk analysis is an iterative process and is conducted at various stages during the development of a particular GMO to **identify and characterise plausible pathways that may lead to harm and to take appropriate actions to mitigate these risks**. The potential risks of GMOs can be mitigated either by (A) decreasing the likelihood of harm or by (B) decreasing the consequence of the harm. Risk mitigation strategies (RMS) are techniques being developed to mitigate potential health and environmental risks of GMOs risks of a particular GMO.

A. Risk mitigation strategies that reduce the likelihood of a potential harm

RMS are under development to decrease likelihood of one or more of the steps of a plausible pathway or scenario that can lead to a harm (Table 1). This will decrease the risk of that particular harm. **Table 1** gives a comprehensive overview of current RMS being developed that will decrease the likelihood of certain potential harms. These strategies have been grouped according to how strategies attempt to reduce the likelihood of identified harms.

Table 1. Overview of RMS in development to reduce the likelihood of risks associated with GMOs.

Strategies that reduce gene flow	
Plastid/Chloroplast transformation	Incorporates transgenes into the plant chloroplast/plastid genome instead of the nuclear genome to reduce gene flow by pollen (Committee on Biological Confinement of Genetically Engineered Organisms, 2004).
Tandem construct	Tandem constructs of genes act genetically as tightly linked genes and their traits are neutral or positive for a crop that would be deleterious to a volunteer weed or wild species (Gressel, 1999).
Engineered male sterility	Pollen development is disrupted and male sterility is induced reducing pollen mediated gene flow. In some cases a restorer system may restore male fertility if required (Dunwell & Ford, 2005).
Conditional lethality	A conditionally lethal gene that is capable of converting a biologically inert toxin precursor into a toxic compound is expressed in transgenic plants, spraying fields with the precursor only kills the transgenic plants and non-transgenic plants are unaffected (Dunwell & Ford, 2005).
Mitigating genes	Mitigation is based on co-inheritance of the transgene of choice, in tandem with a mitigating transgene that renders the weedy recipient unfit to compete with cohorts. This mitigator gene can encode a trait that is either neutral or beneficial to the crop (Gressel, 2010).
Biological containment strategies	Prevent or reduce the spread of transgenic plants/ transgenes they contain outside the areas or species of their intended use by using and/or modifying the plant's innate characteristics, particularly its reproductive characteristics (de Maagd & Boutilier, 2009).
Transient expression	Temporary expression of a transgene in the desired target cells over a relatively short period of time and does not necessarily indicate integration of the gene into the host chromosomes and is not passed onto subsequent generations (Shepherd, 2008).
Strategies that reduce exposure to the transgene	
Transgene excision	Transgene is excised from plants before sexual reproduction, so that the transgene will not spread in the pollen or seeds (Dunwell & Ford, 2005).
Grafting on genetically modified rootstock	The rootstock of a transgenic plant is joined to a scion of non-transgenic plant, thus preventing exposure to the transgene (Committee on the Biological Confinement of Genetically Engineered Organisms, 2004).
Transient expression	Temporary expression of a transgene in the desired target cells over a relatively short period of time and does not necessarily indicate integration of the gene into the host chromosomes and is not passed onto subsequent generations (Shepherd, 2008).
Strategies that reduce exposure to the transgene product	
Recoverable block function	Inseparably links a blocking sequence to the transgene of interest. The "blocker" interrupts a specific function in the host plant that interrupts a molecular or physiological function that leads to lethality in the plant or its seeds. A second sequence element "for recovery" restores the blocked function through an exogenous chemical or physical treatment (Committee on Biological Confinement of Genetically Engineered Organisms, 2004).
Targeted transgene expression	Targets expression of transgene to only those tissues where the expression is required, thus reducing potential and perceived risks, i.e. expression in the roots not in the harvested fruit (Wilkinson et al. ,1998).
Inducible promoters	Transgenes are activated by an artificial stimulus such as a chemical spray. In the absence of the stimulus, the transgene would not express the trait and there will be no conferred advantage to wild or weedy relatives receiving the transgene through hybridisation (Dunwell & Ford, 2005).
Transient expression	Temporary expression of a transgene in the desired target cells over a relatively short period of time and does not necessarily indicate integration of the gene into the host chromosomes and is not passed onto subsequent generations (Shepherd, 2008).

These RMS will only be useful under certain conditions. These include:

- **Decreasing the likelihood of a risk so that activities may take place at an acceptable level of risk.** Fig. 2 illustrates how risks that would not be acceptable under ordinary conditions (indicated by horizontal shading) are mitigated to levels that are generally considered as acceptable. These may be applicable where:

  -a risk has been characterised but the overall level risk is considered unacceptable
  -additive risk mitigation features decrease the likelihood of risk. A RMS may be included into an integrated risk management plan where the cumulative reduction of risk will result in the activity taking place at an acceptable level of risk.
  -the need for other risk mitigation can be decreased. The RMS, e.g. engineered male sterility, may decrease the need for other risk mitigation measures employed during activities with the GMO, e.g. separation distances or monitoring for feral populations.

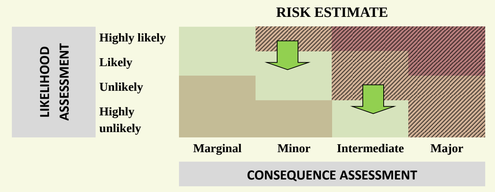

Figure 2. Decreasing the likelihood of a risk so that activities can take place at an acceptable level of risk.

- **Where the RMS will decrease regulatory information requirements.** In instances where the necessary information to make a regulatory decision is lacking and /or difficult to generate it is possible to decrease the likelihood of the risk so that activities may still proceed within an acceptable level of risk. This may be achieved in two scenarios where:

  -there is uncertainty with regards to the likelihood of the event, e.g. if it is uncertain whether the likelihood of an event is 'highly likely' or 'likely' where the consequence has been characterised as 'minor'. This will give an overall risk estimate of 'moderate' or 'low'. A suitable RMS may then be employed to decrease the likelihood of the event (without necessarily decreasing the uncertainty) so that the activity may take place with an acceptable level of risk (see Fig. 3).

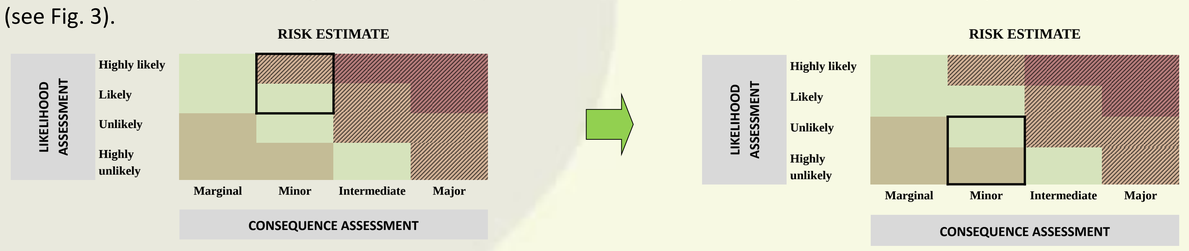

Figure 3. Decreasing the likelihood of the risk when there is uncertainty with regards to the characterisation of likelihood (blocked) so that activities can take place at an acceptable level of risk.

-there is uncertainty with regards to the consequence of the event, e.g. if it is uncertain whether the consequence of an event is 'minor' or 'intermediate' if the likelihood is decreased to 'highly unlikely' then the activity may proceed with an acceptable level of risk (i.e. negligible or low; see Fig. 4).

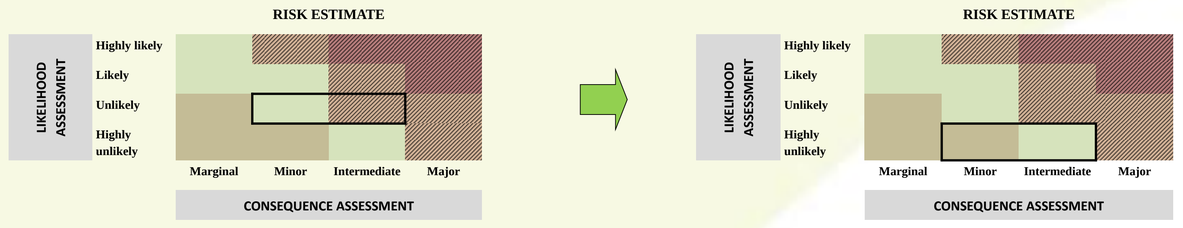

Figure 4. Decreasing the likelihood of the risk when there is uncertainty with regards to the characterisation of consequence (blocked) so that activities can take place at an acceptable level of risk.

B. Risk mitigation strategies that reduce consequence

Risk can also be mitigated by **decreasing or removing potential harms (and hence consequence) relative to standard existing methods** as the scope for changing the inherent consequence of a particular GMO is limited (see Fig. 5). MicroRNA mediated resistance as a RMS compared to protein based resistance will reduce the harms associated with protein products. Another example includes cisgenetics as a RMS to reduce theoretical harms associated with the introduction of novel genetic material into an organism. However, these technologies will only be useful in decreasing risk where clear harms and pathways to harm have been identified. These technologies may also be useful at decreasing regulatory requirements where there is uncertainty and or diverging views with regards to a potential harm or a plausible pathway to harm.

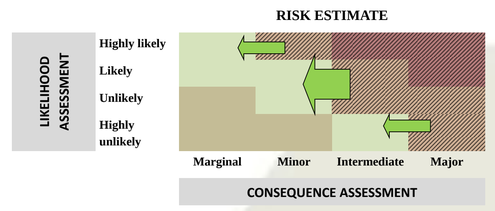

Figure 5. Decreasing the harm (and hence consequence) of a risk relative to existing methods so that activities can take place at an acceptable level of risk.

Discussion

- The majority of these RMS **need to be incorporated early** on in the research and development of a particular product.
- The process of problem formulation and risk assessment must take place early on in the development of the product to identify and define **clear harms and plausible pathways to these harms**.
- The rationale behind how the RMS will decrease identified risk or assist with decreasing regulatory requirements must be clearly elucidated.
- It is recommended that the process of **problem formulation must take place in conjunction with the regulators** as the definition of harm requires regulatory input. This would ensure that clear harms are identified and assist in efficient regulatory decision making and product development.
- A **risk assessment is highly dependent on the chosen risk assessment matrix** and definitions of likelihood and harm. South Africa has not adopted an appropriate risk assessment matrix. This may hinder sound regulatory decision making. This will apply more widely to risk assessment of GMOs and not just the use of RMS to mitigate risks of GMOs.

Recommendations

- Adoption of a risk assessment matrix and definitions of likelihood and consequence assessment are critical for a risk assessment process.
- Problem formulation forms an integral part of any GMO risk assessment.
- The use and application of RMS will require a well integrated system where there is communication between regulators and developers of the GMO.
- The developer of the technology must conduct an 'a priori' risk analysis and describe clearly what risks or uncertainties the particular RMS is addressing.

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