Biosafety Unit

Biosafety risk assessment: The problem formulation approach

Wendy Craig

Scientific Co-ordinator
ICGEB Biosafety Unit
craig@icgeb.org

www.icgeb.org/biosafety

Biosafety Unit

GMO Regulation

Countries usually have a **legislative scheme** regarding the use of novel technologies and/or their products

e.g. Cartagena Protocol on Biosafety states that before a LMO/GMO is released into the environment, **a determination of the possible associated risks** to the environment, including to human health, should be undertaken

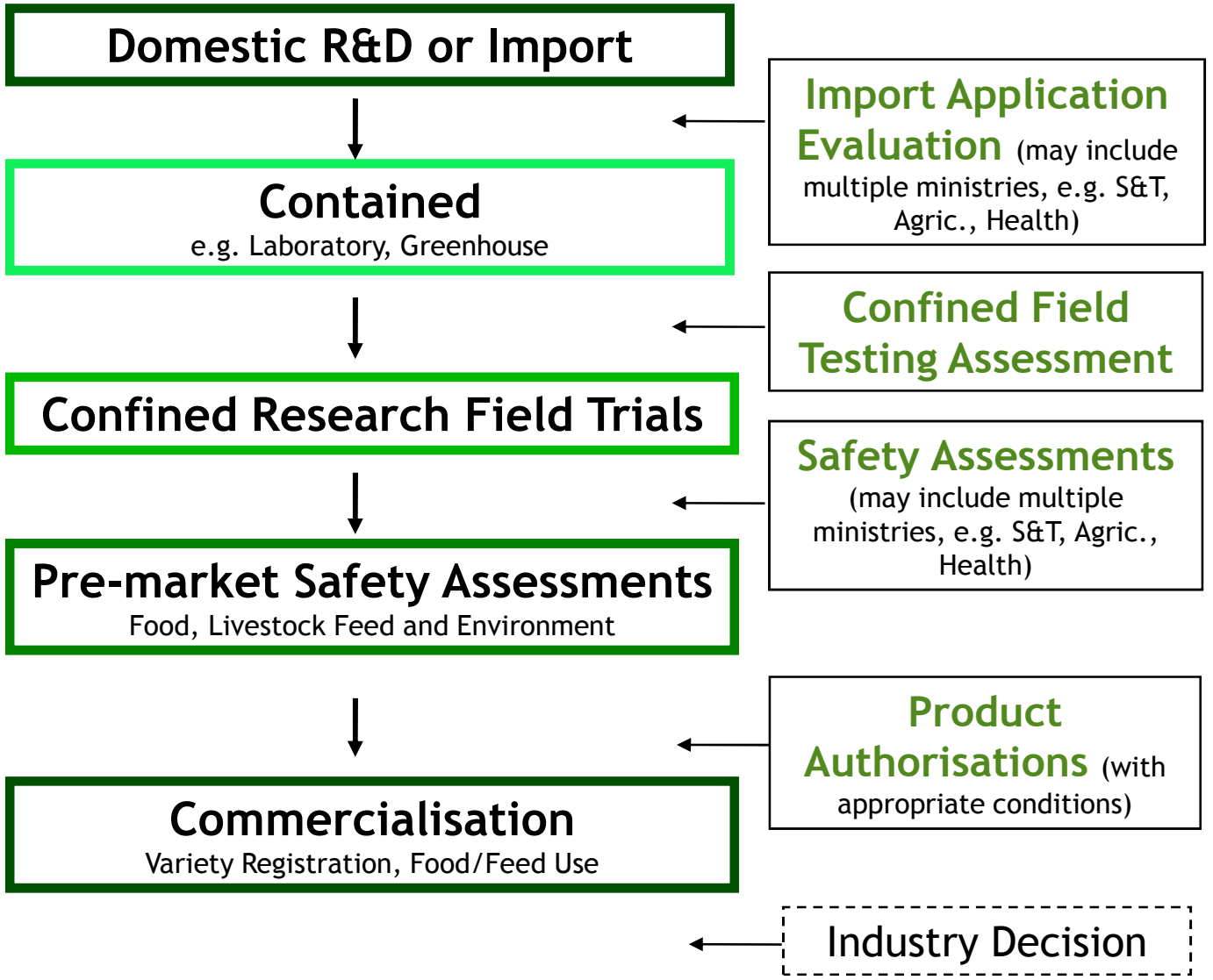
Genetically Modified Organisms will therefore fall under the remit of a **regulatory process**

Various scientific and technical approaches (e.g. Risk Assessment) have been developed **to assist the decision-making process** regarding the possible permitted use of biotechnology and/or its products

Regulation **oversees all stages** of permitted use (see next slide)

Biosafety Unit

Product Development and Regulatory Stages



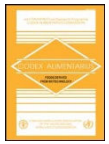
Biosafety Unit

International Guidelines

CODEX ALIMENTARIUS COMMISSION

FAO/ WHO Food Standards
CODEX alimentarius

Foods Derived from Biotechnology, 2009.



Foods Derived from Biotechnology, 2004. Incorporating:
- Principles for the Risk Analysis of Foods Derived from Modern Biotechnology, 2003;
- Guidelines for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants, 2003;
- Guidelines for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms, 2003.

JOINT FAO/WHO EXPERT CONSULTATIONS

Safety Assessment of Foods Derived from Recombinant-DNA Animals, Feb-Mar 2007

Safety Assessment of Foods Derived from Genetically Modified Animals, including Fish, November 2003

Safety Assessment of Foods Derived from Genetically Modified Microorganisms, September 2001

Evaluation of Allergenicity of Genetically Modified Foods, January 2001

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

OECD

Considerations for the Safety Assessment of Animal Feedstuffs derived from Genetically Modified Plants (2003)

Report of the Task Force for the Safety of Novel Food and Feeds (2000)

Safety Considerations for Biotechnology Scale-up of Crop Plants (1993)

Recombinant DNA Safety Considerations (1986)

OECD "Blue Book"

UN ENVIRONMENT PROGRAMME

UNEP

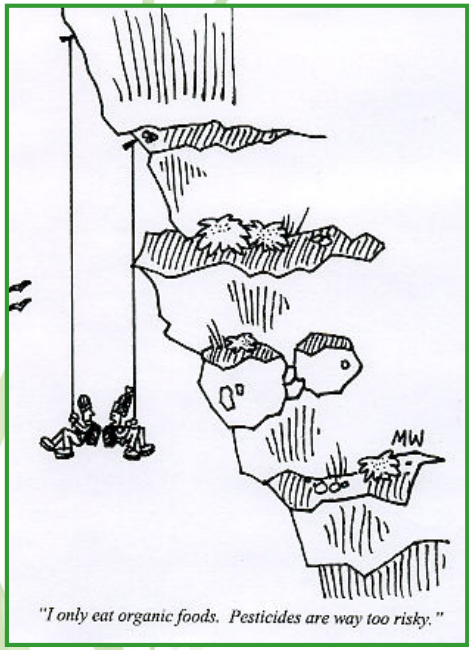
UNEP International Technical Guidelines for Safety in Biotechnology (1995)

Biosafety Unit

Risk Analysis to Assist Decision-making

In the broadest sense:

Risk analysis = risk assessment + risk management + risk communication



Risk assessment (RA) – identifies sources of potential harm, assesses the likelihood that harm will occur, and the consequences if harm does occur

Risk management (RM) – evaluates which risks identified in the RA require management and selects and implements the plans and actions required to ensure those risks are controlled

Risk communication - involves an interactive dialogue between stakeholders and risk assessors and risk managers to actively inform the RA and RM processes

Biosafety Unit

Placing Impacts in Context

Some authorities, e.g. CFIA, use a comparative approach –

Does the addition of this GM crop cause a greater impact than the unmodified crop?

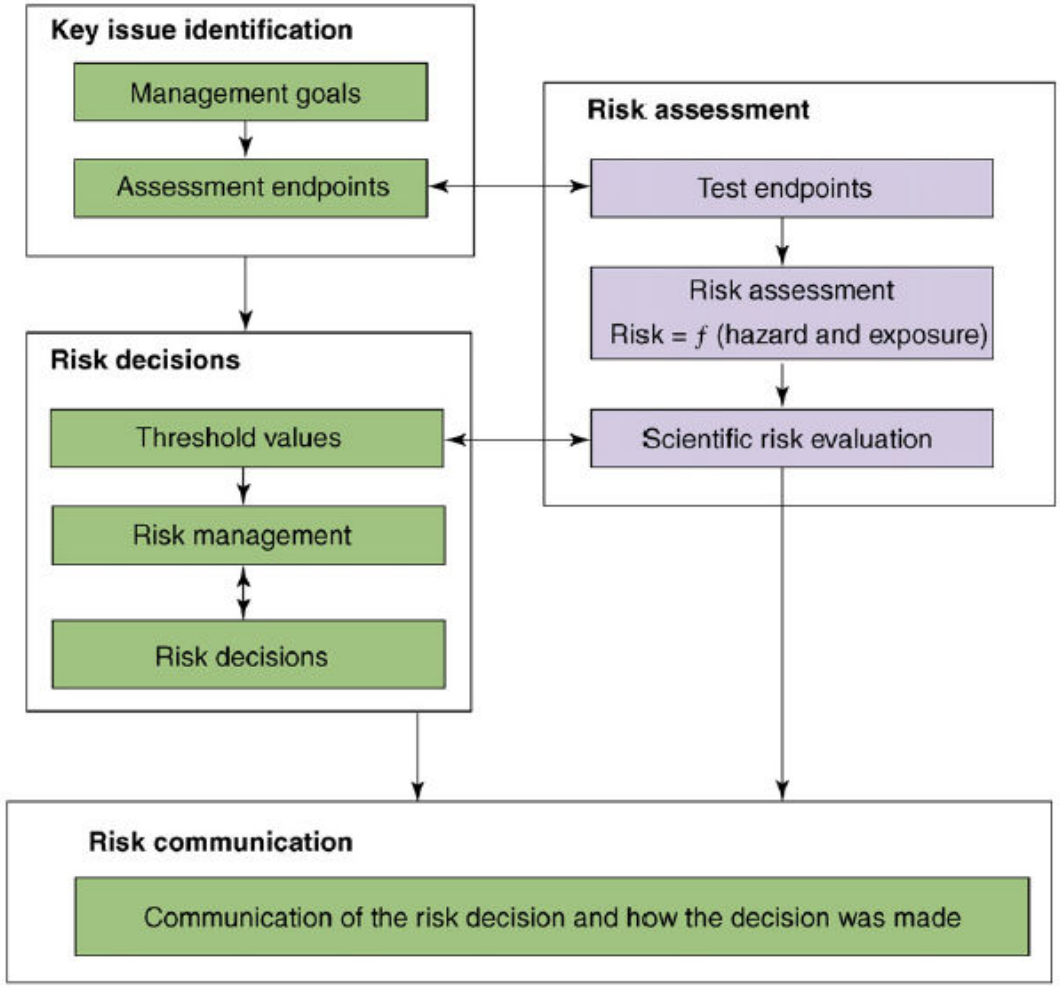
Example: Canada grows 10-12 million acres of canola (oilseed rape) each year – this has an impact on biodiversity

- Macroscopic perspective - Does the impact of a herbicide tolerance gene in canola cause a greater impact on biodiversity?
- Microscopic perspective - A canola plant has thousands of genes – what is the impact of an additional gene?

Biosafety Unit

Risk Analysis to Assist Decision-making

Loaded with unfamiliar terminology!!!



Stages of risk analysis:

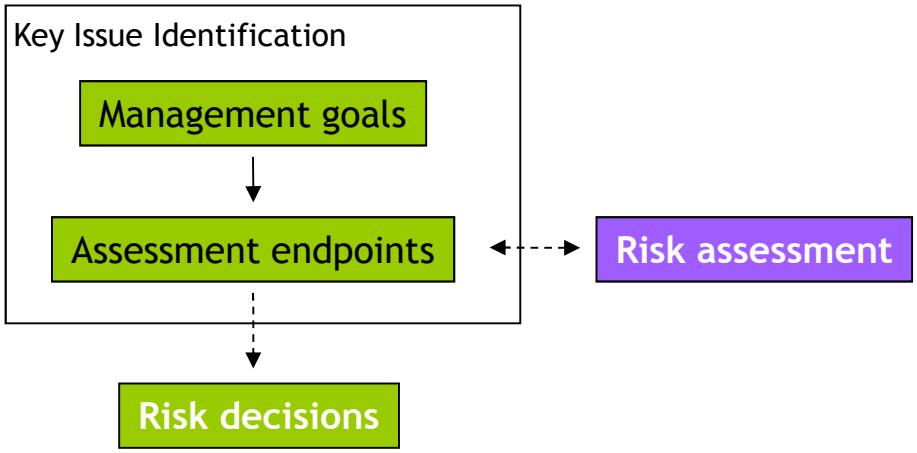
key issue identification, **risk assessment**, **risk decision-making** and **risk communication**. Progression through the system is not linear, but iterative. Feedback loops, although not included in this diagram, are an integral part of risk evaluation.

Green boxes - driven by society; Purple boxes - driven by science

KL Johnson, AF Raybould, MD Hudson & GM Poppy, 2007. Trends in Plant Science 12(1): 1-5.

Biosafety Unit

Key Issue Identification



What are Management Goals?

Will derive from legislation - typically "protection of the environment" and/or "to protect the health and safety of people" - **'Protection Goals'**

What are Assessment Endpoints?

The identification of assessment endpoints is the most difficult, but most crucial, component of risk analysis – **'What we don't want to be harmed'**

Should have specific targets that **can be analysed scientifically**, e.g. the population size of a given legally-protected wild species.

How to make sense of this formative step in risk assessment?

The answer? PROBLEM FORMULATION .....

Biosafety Unit

Problem Formulation

Main objective of workshop -

Teach a practical approach based on Problem Formulation, to help link the policy objectives that drive risk analysis to the assessment of the potential impact(s) of the dissemination of specific GMOs.

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 are.

Biosafety Unit

Problem Formulation

Steps of problem formulation approach:

(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

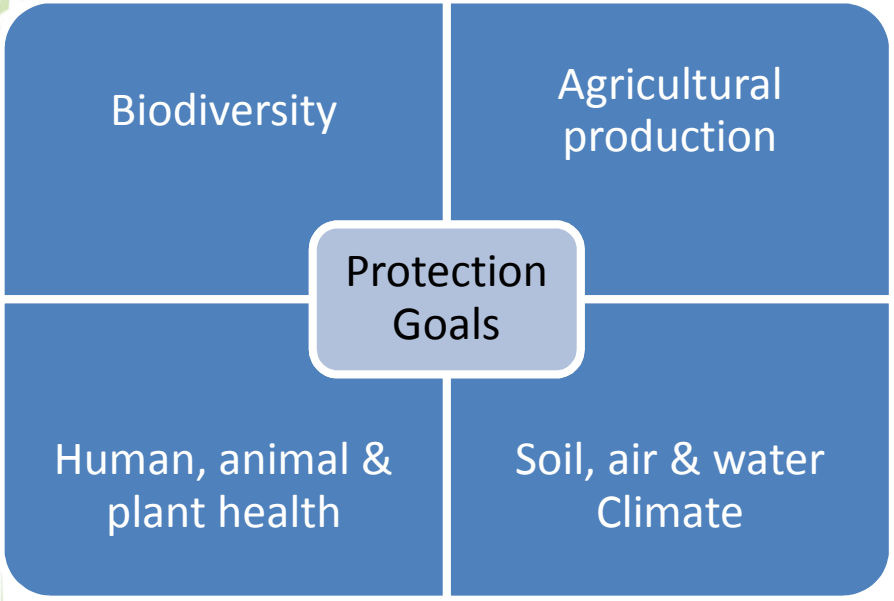
(8) Risk assessment

Tepfer, Racovita & Craig, 2013. Putting problem formulation at the forefront of GMO risk analysis. *GM Crops and Food: Biotechnology in Agriculture and the Food Chain* **4(1)**: 1-6

Biosafety Unit

1 - The 'problem' with Protection Goals

Protection goals are usually defined by regulations as part of national policies, and often formulated in legal terms using normative concepts such as "sustainability, integrity, acceptability,…"



Problems:

- Can be widely interpreted
- Often impossible to prove or falsify
- Too vague to be scientifically assessed

Biosafety Unit

2 - Undesirable Harms – Definitions

- No consensus exists, but proposed definitions of harm feature:
  i. damage to a resource (for example, a reduction in the conservation or sustainable use of biodiversity);
  ii. an adverse change that is either significant or severe or that exceeds the natural range of variability; and
  iii. is measurable (or predictable).
- Leads to three main questions when defining harm:
  i. What needs to be protected?
  ii. What is meant by "adverse"? and
  iii. What is to be measured, and for how long, in order to predict the likelihood that harm will occur?
- Involves the political/societal process of setting the pertinent baselines for comparison and thresholds when performing risk assessments.
- **What about benefits???**

2 - Example of Developing Harms

Biosafety Unit

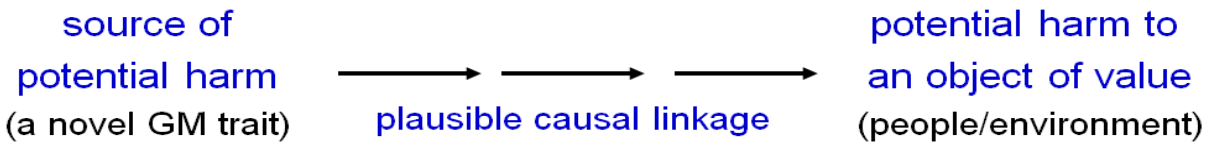
① Protection goals		② Assessment endpoints						③ Measurement endpoints		
		Criteria for the operational definition of the protection goal						Criteria for the type of effect to be measured		
Area of protection		Ecological entity	Attribute	Unit of protection	Spatial scale of protection	Temporal scale of protection	Definition of harmful effect	Indicator	Parameters Early tiers	Parameters Higher tiers
Biodiversity conservation	Red List species Species of high conservation / cultural value	Mammals	Abundance				Relevant decrease in abundance	Selected species		
		Birds								
		Amphibians								
		Valued insects (e.g. butterflies)		Population	Non-agricultural habitats	10 years			Mortality	Abundance
		Valued plants								
	Protected habitats	Habitats listed in legislation						Selected habitats		
Ecosystem services	Pollination	Pollinating insects	Ecological function	Guild	Arable land and non-agricultural habitats	Following cropping season	Relevant disturbance in ecological function	Direct or indirect indicator able to demonstrate failures in ecosystem function	Mortality	Abundance
	Pest regulation	Predators & parasitoids								
	Decomposition of organic matter	Soil invertebrates, soil microorganisms		Guild	Crop fields	Following cropping season			Decomposition rate	Abundance
	Soil nutrient cycling (N, P)	Soil microorganisms								
	Soil structure	Soil invertebrates								
	Water regulation and purification	Fish								
		Aquatic invertebrates								
		Algae								

Sanvido *et al.*, 2012. Evaluating environmental harms of GM crops: ecological harm criteria for regulatory decision-making. *Environmental Science & Policy* **15**: 82-91

Biosafety Unit

3 - Risk hypothesis

- A risk hypothesis simply joins a cause and an undesired effect.
- Essentially, re-states harms as risk hypotheses in the form of declarative sentences that describe exactly what could be harmed and how this would occur.
- Transforming loosely-worded concerns into clearly-stated testable risk hypotheses is the heart of problem formulation.
- Can be negative or positive statements.

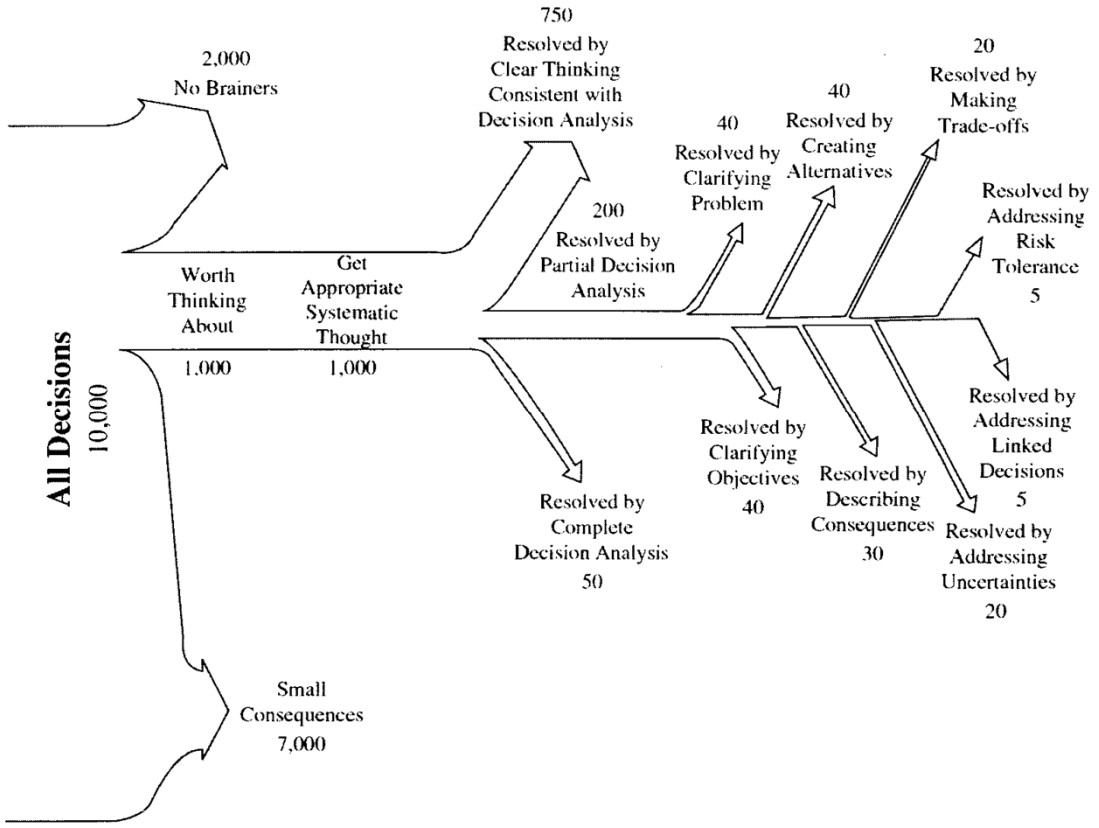


Examples from previous workshops (Bt cotton case study):

- Oil and cottonseed cake from Bt cotton will cause allergic reactions or toxicity in humans or animals
- The development of pest resistance to Bt cotton will lead to increased cost of bollworm control
- The Bt gene will introgress into wild species, creating new weeds
- Exposure to Bt protein will lead to compromised sexual prowess and infertility in farmers and consumers

Biosafety Unit

4 - Prioritisation / Triage



From a general perspective, only a small proportion of the issues involved in a complex decision-making process may need in-depth consideration.

Prioritisation creates a short loop for removing certain potential harms from further consideration, without going through the process of creating a detailed pathway to harm

Keeney, 2004. Making better decision makers. *Decision Analysis* **1**: 193-204.

Biosafety Unit

5 - “Pathway to harm” - Conceptual Model

- The pathway to harm, sometimes referred to as a “conceptual model” or “scenario”, 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.
- Each step must be formulated in a way that can be evaluated in the light of data.
- Careful scrutiny of the pathway to harm can identify which steps may be most decisive in attempting to break the pathway, even before considering the data that may be pertinent to testing the risk hypothesis.
- The power of this approach is that it suffices to break only 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.

Biosafety Unit

5 - “Pathway to harm” - Conceptual Model

Example - A crop wild relative becomes more invasive due to introgression of transgene (after Lu, 2008)

Crop wild relative (CWR) grows in the vicinity of GM crop

↓

CWR flowers simultaneously with GM crop

↓

GM crop naturally hybridises with CWR

↓

Frequency of pollen-mediated gene flow is not extremely low

↓

Transgene expresses normally in CWR

↓

Increase in fitness of CWR

↓

Change in CWR population dynamics through increased invasiveness

Biosafety Unit

6 - Test the Risk Hypothesis

- Identify key steps in pathway, and add available data where pertinent
- Determine if the existing data break the pathway
- If not, identify what additional data would allow satisfactory testing of the hypothesis

Risk hypothesis: Cultivation of DT maize leads to loss of genetic diversity in landraces

DT maize is planted in same area as the conventional maize – **YES**

Farmers prefer growing DT maize to conventional maize – **INFORMATION ON FARMER PREFERENCES**

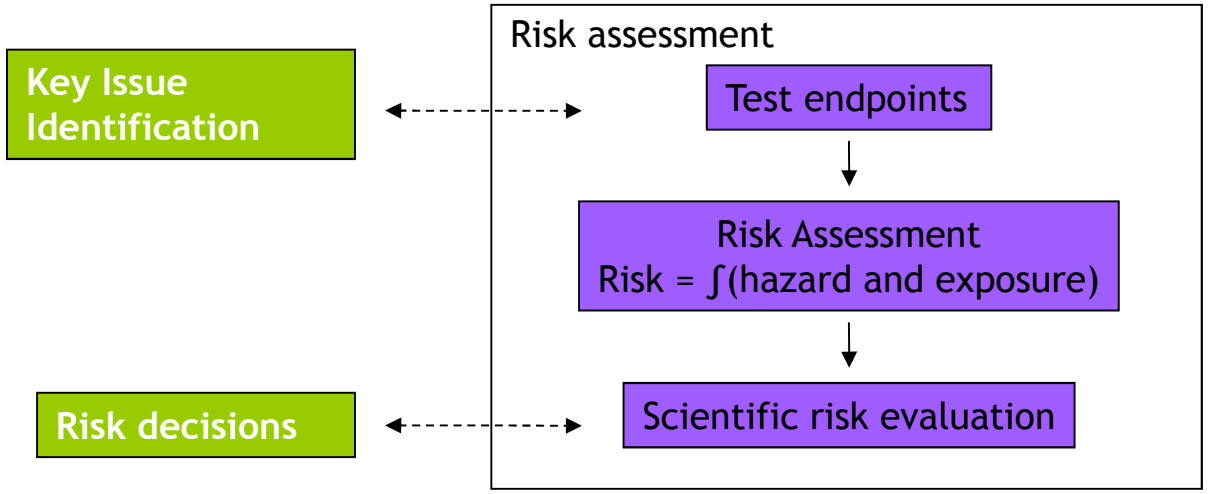
With time farmers will stop growing certain/all landraces - **LIKELY**

Farmers do not store or multiply their landraces to maintain viability - **UNLIKELY**

Loss of landraces and hence genetic diversity - **UNLIKELY**

Biosafety Unit

Risk Assessment (RA)



Risk assessments should be:

- science-based
- carried out on a case-by-case basis
- comparative
- iterative

Planning a risk assessment for the GM crop must consider the nature of the trait, the nature of the crop, the likely receiving environment and the interaction(s) amongst these.

Biosafety Unit

Risk Assessment

Incorporates two phases:

1) a comparative analysis with the non-GM counterparts to identify any differences*, followed by

2) an assessment of the environmental and food/feed safety or nutritional impact of the identified differences, including both intended and unintended differences

The sequential steps in the safety/risk assessment of GMOs comprises:

- **hazard identification** - identify characteristics which may cause adverse effects
- **hazard characterisation** - evaluate their potential consequence
- **exposure assessment** - assess the likelihood of occurrence
- **risk characterisation** - estimate the risk posed by each identified characteristic

*Statistically significant differences may point to biological changes caused by the genetic modification, but these may/may not be meaningful in terms of harm to humans, animals and the environment. It is therefore critical to not only evaluate the scientific quality and validity of studies used to inform risk assessments, but also to consider their relevance to risk assessment.

Biosafety Unit

Risk Assessment

To conclude the risk assessment, evaluations are undertaken to judge the significance of the various risks, and, based on a weight of evidence approach, an evaluation of the overall risk.

A useful tool is a “risk matrix” to help estimate the level of risk

		LEVEL OF RISK			
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			

Biosafety Unit

Risk Management (RM)

While RA deals as far as possible with **objective evidence**, risk management necessarily involves **prudential judgements** about which risks require management, the choice and application of treatment measures, and ultimately whether the application should be permitted

RM therefore builds on the work of the RA, and can be formulated as -

Does anything need to be done about the risk?

What can be done about it?

What should be done about it?

While the focus is on prevention, it should also address how to manage adverse outcomes if a particular risk is realised -

Can adverse consequences be reduced/reversed?

Are measures available that can achieve these ends?

These can be incorporated into the licence conditions or contingency plans

Biosafety Unit

Risk management approach

N.B.

There is a crucial distinction between **confined trials** and **unconfined environmental releases**

At the level of a **confined** trials, the risks may not yet be fully understood without data collected during the trial, hence the focus must be on **risk prevention** – the terms and conditions that are necessary to permit safe trial conduct

Conversely, for an **unconfined** release, the focus must be on **rigorous risk assessment** as the intent is widespread introduction of the modified plant into agriculture, usually with few or no restrictions

Biosafety Unit

Risk Management (RM)

The “phased approach” enables information to be collected about the GMO at each stage in order to **reduce uncertainty** in the risk assessments, and to **confirm the efficiency** of containment measures

This information **may result in changes** to licence conditions to better manage risks and will inform future evaluations of the same or similar GMOs

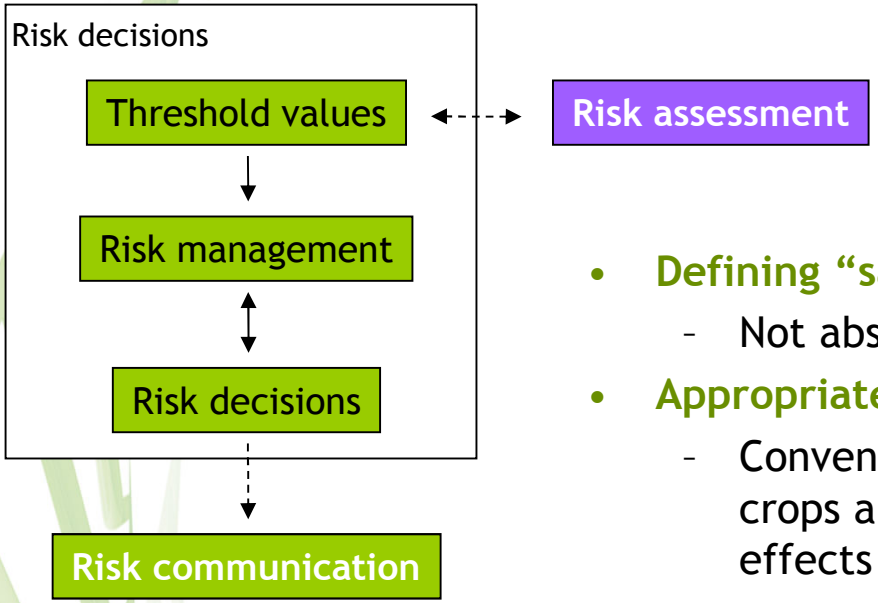
Monitoring is essential to ensure compliance with any licence conditions to ensure that risk management requirements are being implemented

Biosafety Unit

Risk Decisions

Challenges:

- **Reasonable certainty**
  - Zero risk does not exist, therefore we must explicitly or implicitly accept some level of uncertainty
    - GM crops can not be made safer than biology itself. Rather, are the risks acceptable?



- **Defining "safe"**
  - Not absolute, but relative, safety: "as safe as"
- **Appropriate comparators**
  - Conventional agriculture and traditionally bred crops are the usual baseline from which to evaluate effects
- **How much data are sufficient for decision-making?**

"need to know vs. nice to know"

Biosafety Unit

Risk Decision

After the Assessment

You'll never have all the answers you need, so…….

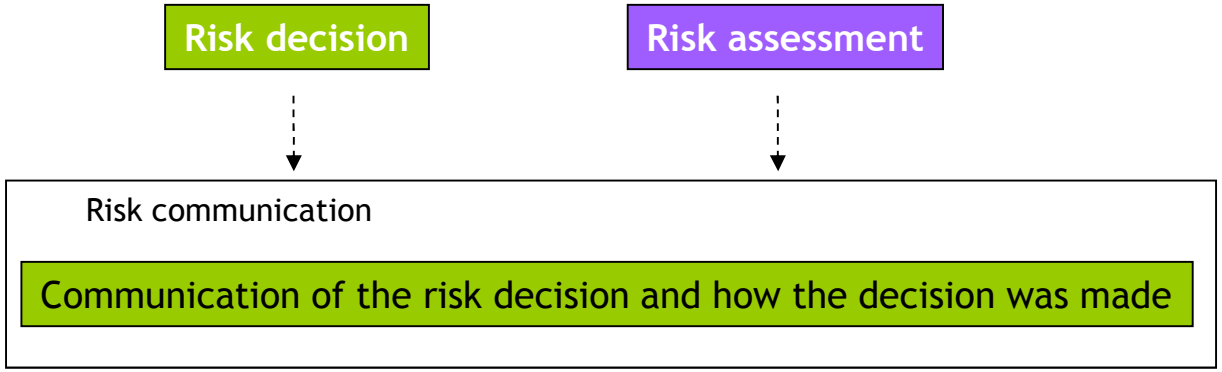
What is the acceptable threshold for risk ?
What management options are available ?

Final decision on acceptable risk is related to socio-economic and cultural goals

- Ask for more information
- Approve, based on available knowledge
- Approve, imposing reasonable risk management conditions
- Refuse approval if the product poses an unacceptable risk (or application may be withdrawn)

Biosafety Unit

Risk Communication



Risk communication **underpins** the RA & RM processes

Establishes an interactive dialogue between the decision-makers and stakeholders to provide **open, transparent & consultative** risk-based regulation of GMOs

Trust in information and **the information provider** is an essential element in ensuring effective risk communication

Should not be seen as the last element in a linear process, but as a vital element of the whole risk analysis process

Should include **an explanation** of the risk assessment findings and of the basis of risk management decisions

Members of the Biosafety Unit:

Decio RIPANDELLI
Head of Biosafety Unit

Cape Town
Dennis OBONYO
Stephnie SMITH

Trieste
Wendy CRAIG
Francesca FAROLFI
Monica RACOVITA

Rome (Italian BCH)
Anna RUSSO

New Delhi
Vanga Siva REDDY

www.icgeb.org/biosafety