Canadian Food Inspection Agency | Agence canadienne d'inspection des aliments

Canadian Food Inspection Agency




Our vision:
To excel as a science-based regulator, trusted and respected by Canadians and the international community.

Our mission:
Dedicated to safeguarding food, animals and plants, which enhances the health and well-being of Canada's people, environment and economy.

Unconfined Environmental Release Assessments of Plants with Novel Traits

Phil Macdonald
Biotechnology Environmental Release Assessment Unit (BERA)

Canada

Outline

- Regulating biotechnology- starting with science- How did we get here?
- Canada's take on regulations- how science changed Canada's regulatory thinking about biotechnology
- Some definitions
- Risk Assessment concepts
- How we address unintended effects
- Why we are here
- Conclusions

Science Based Regulation for GMOs- the early days

‘***Blue Book’: Recombinant DNA Safety Considerations, OECD 1986***

Authors

- scientists, academia, advisory committees
- scientists, regulators
- representatives of governments
- representatives of industry

Science Based Regulation for GMOs- the next steps

Safety Considerations for Biotechnology, OECD 1992

- Outlined safety assessment guidance for products of biotechnology
- Captured some key principles such as basing the safety assessment on a comparison with the unmodified counterpart
- Focus on the new trait in the plant
- Avoided defining biotech

Canada's Regulatory Route

- The framework for the regulation of biotechnology products in Canada was established in 1993. The framework relies on using existing legislation and regulatory bodies to regulate biotechnology products (i.e. they are regulated under the same broad legislation that is in place for food, feed and seed)
- Regulation should be based on the product not the process
- The framework also recognizes that regulations should be put in place that allow innovation to proceed while protecting the health and safety of Canadians and the environment
- Clear signal of how biotechnology is regarded as a technology

Regulatory Trigger in Canada

Plants with Novel Traits (PNTs)

Not specifically plants modified by recombinant DNA techniques

e.g. herbicide tolerant plants - similar environmental risk issues whether derived from rDNA, mutagenesis or traditional breeding

- *There are commercial herbicide tolerant canola varieties that have been developed by all of these methods- risk assessment consideration are the same*

Some Definitions

From the Canadian Centre for Occupational Health and Safety:

- Hazard- any source of potential damage or harm
- Risk – the probability that harm will result
- Harm- the negative outcome from the hazard

Risk = Hazard X Exposure

Conceptual Model

Conceptual models form the framework for our risk assessments

Defintion: Descriptive model of a system based on qualitative assumptions about its elements, their interrelationships, and system boundaries.

Our conceptual model for biotech crops has been developed over many iterations and forms the basis for our assumptions during a risk assessment

For an environmental risk assessment, the conceptual model will consider the crop, the new trait, the likely receiving environment and pathways by which an effect is likely to occur

Conceptual Model

Our assessments uses a “familiar” counterpart as a reference

- relies on “substantial equivalence to define acceptable harm”
- these concepts are adapted from OECD food safety assessment criteria and applied to both environmental, food and feed safety assessment
- very effective for crops and traits we know well

Safety Assessment Concepts:

Familiarity:

The knowledge of the characteristics of a plant species and experience with the use of that plant species in Canada

- Biology documents are the basis for the comparative risk assessment

- Knowledge of (agricultural) ecology is the assessment context for a crop species

Safety Assessment Concepts

Substantial Equivalence:

The concept of comparing new products with existing familiar products

Definition from the regulations:

The equivalence of a novel trait within a particular plant species, in terms of its specific use and safety to the environment and human health, to those in that same species, that are in use and generally considered as safe in Canada, **based on valid scientific rationale**

Comparative Assessments of PNTs

- Risk assessment considers relative safety of the product in both the short and longer term
- Comparative
  - Information about the novel plant is compared to information known about the biology of the counterpart
- Considers the expected trait in the context of the unmodified plant and considers how it can effect things we value by using indicators we can measure
- In this structured analysis how do we account for “unknown unknowns” which could include unintended effects

Unintended Effects

- Genetic engineering conducted with a specific objective in mind
- The aim is to transfer foreign DNA into a host organism and effect specific changes within that organism.
- For example, the plant may be meant to become herbicide- or pest-resistant
- Unintended effects are those that appear in addition to the intended results.
  - E.g. altered version of an enzyme in a metabolic pathway may have effects on related pathways
  - Insertion of the new gene disrupts an endogenous gene, reads through to create a chimeric protein
  - Downstream effect on another gene or cryptic ORF

Unintended Effects

- We know that unintended effects are possible
- Where does this fit into our risk assessment approaches
- Many regulatory systems consider unintended effects important enough that they regulate every transformation event or “stacked event”
- How do we address these types of phenomena in the risk assessment and how important are they?

Risk Assessment

Hazard

+

No exposure

= No risk

Hazard + exposure =

Risk

Hazard Identification

- Identify potential hazards
- Failure to engage in proper hazard identification can compromise the entire risk assessment and lead to inadequate or unnecessary risk management decisions
- Endpoints are value driven and set by policy (eg. The protection of an endangered species), the process to assess harm to an endpoint should be firmly based in science and hypothesis driven
- Comparative safety assessments should be based on reasonable risk hypotheses that focus on realistic potential harm
- Just having a difference doesn't necessarily mean a harm

Exposure Assessment

- Exposure assessment is the determination or estimation of the route, amount, frequency, and duration of exposure (Peterson- 2011)
- For unconfined release exposure is generally considered to be uncontrolled i.e. in the environment, no longer subject to conditions-
- Although some data is quantitative, (toxicology), the assessment is primarily qualitative i.e. “safe as”

Tiered Approaches

- The comparative risk assessment proceeds in a structured manner based on the risk hypothesis
- Laboratory tests will often identify the worst case scenario
- If the first tier of testing does not identify a risk, then the assessment should stop- can apply to all scenarios
- This data can be quite portable

Unconfined Release

Assessment Focuses on:

- the novel trait
- the novel plant characterization
- the novel plant interactions
- changed agricultural-silvicultural practices

As it Effects (5 pillars):

- altered weediness potential
- gene flow to related species
- altered plant pest potential
- potential impact on non-target organisms
- potential impact on biodiversity

Assessment process - 5 months with complete information

Unconfined Release

- Risk assessment concentrates on the intended trait
- Where unintended effects can be anticipated e.g. changes to metabolic pathways or interactions with endogenous proteins, risk hypotheses can be constructed
- Unexpected effects more difficult to address so risk assessment tends to concentrate on phenotypic characterization
- Genomics can lead risk assessors down unproductive routes without a clear hypothesis

Weight of Evidence in Risk Assessment

Weight of Evidence as a Methodology

- Based on the data and referring to the risk hypothesis, what is the reasonable conclusion
- Implies an examination of all available evidence, positive and negative, consideration of data quality and weighing studies to arrive at a reasonable conclusion
- What standard of proof do we require? Do we even know and is it consistent?

Weight of Evidence in Risk Assessment

Assessing Information With a Weight of Evidence Consideration

- Relevance- how relevant is that piece of data to making a hypothesis probable-
- Reliability- How reliable is the data- well replicated experiments, proper controls
- Sufficiency- what is the threshold of weight ?????? -need to know vs. nice to know

Weight of Evidence in Risk Assessment

Context in the Conceptual Framework

- Difficult to predict but not impossible
- As an iterative process need to rely on experience and previous data to build a body of evidence on which we can rely- are we doing that?
- Wide variety of data requested for food, feed and environmental assessments – are we adding precision or just more uncertainty

Weight of Evidence in Risk Assessment

Implementing weight of Evidence Approaches

- Are we using weight of evidence approaches in a systematic and consistent way?
- Are we taking advantage of the experience and body of evidence that we have accumulated over more than 10 years of assessments on similar products?
- Are our questions hypothesis driven- have we identified and understood the endpoints we are protecting, do we have a reasonable risk hypothesis
- Have we engaged properly with risk managers/decision makers in the problem formulation step?

Putting Unintended Effects into Context

Scientific consensus that genetic engineering is not risky

"the World Health Organization, the American Medical Association, the U.S. National Academy of Sciences, the British Royal Society, and every other respected organization that has examined the evidence has come to the same conclusion: consuming foods containing ingredients derived from GM crops is no riskier than consuming the same foods containing ingredients from crop plants modified by conventional plant improvement techniques."

(From the AAAS Board Report 2012)

Can We Learn From Our Experience?

- Increased familiarity with GE plants, foods and feeds
- Growing body of scientific research on genetic engineering
- In particular, advancements in molecular analysis techniques has given us an unprecedented understanding of plant genomes and genetic change
- As a first step, consider insertional effects

Evaluation of a Transgenic Plant Intended for Commercialization

Molecular characterization of the PNT

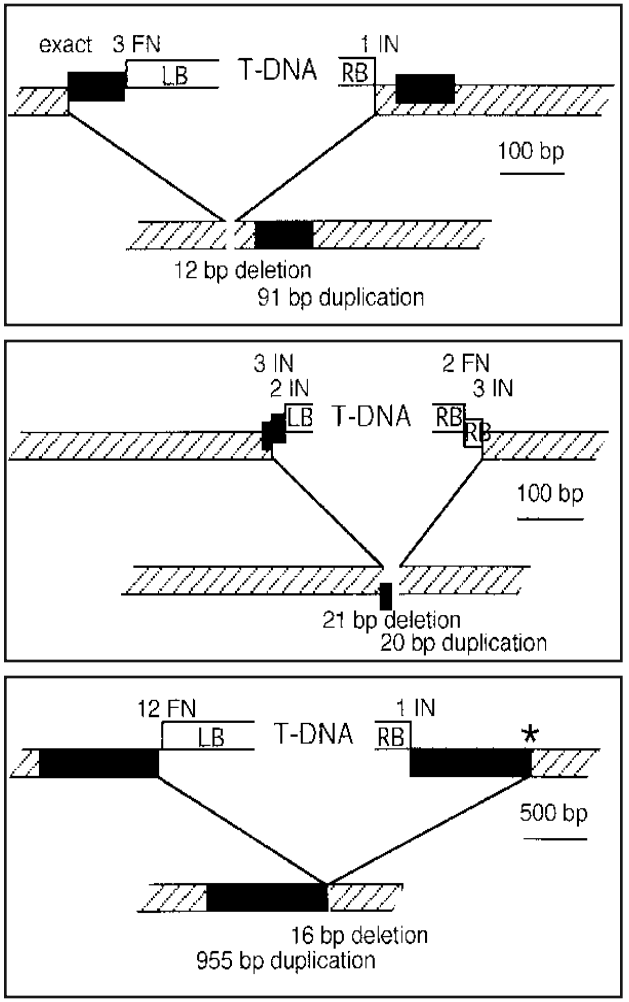
- Common element for the safety assessment for food, feed and environmental release
- Not the entire assessment but informs all aspects of the assessment
- Complete molecular characterization can reduce of eliminate uncertainty in other aspects of the assessment e.g.
  - routes of exposure
  - levels of expression
  - presence or absence of new proteins

The insertional effects project

- Review insertional effects and their potential to result in unintended traits
- In keeping with the comparative approach, compare insertional effects to other types of genetic changes in plants
- Has our understanding evolved sufficiently to re-evaluate the criteria required for the pre-market assessment of GE plants, foods and feeds?

What are insertional effects?

- Changes to the transformed plant's genome that result from the process of inserting DNA by genetic engineering
- May include:
  - Insertion of "intended" DNA
  - Insertion of additional DNA
  - Deletions
  - Rearrangements
- Insertional effects can result in the expression of unintended traits

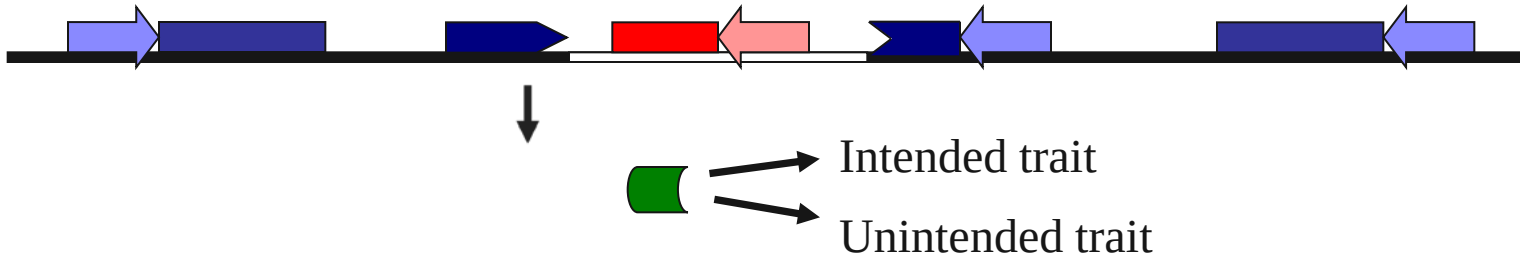


Forsbach et al. 2003. Plant Mol Biol 52: 161-176

Insertional effects are not….

Pleiotropic Effects

- Single gene within the inserted DNA confers multiple traits



Position Effects

- Variations in the expression of genes within the inserted DNA that are dependent on the site of insertion

The insertional effects project

- Insertional effects are an unavoidable consequence of genetic engineering, but the introduction of unintended traits is not
- Genetic changes similar to insertional effects occur during:
  - The movement of transposable elements
  - The repair of double-strand breaks by NHEJ
  - The transfer of organelle DNA to the nucleus
- Plant genomes are constantly changing, and insertional effects will make a relatively small contribution to the final genetic make-up of a given plant variety

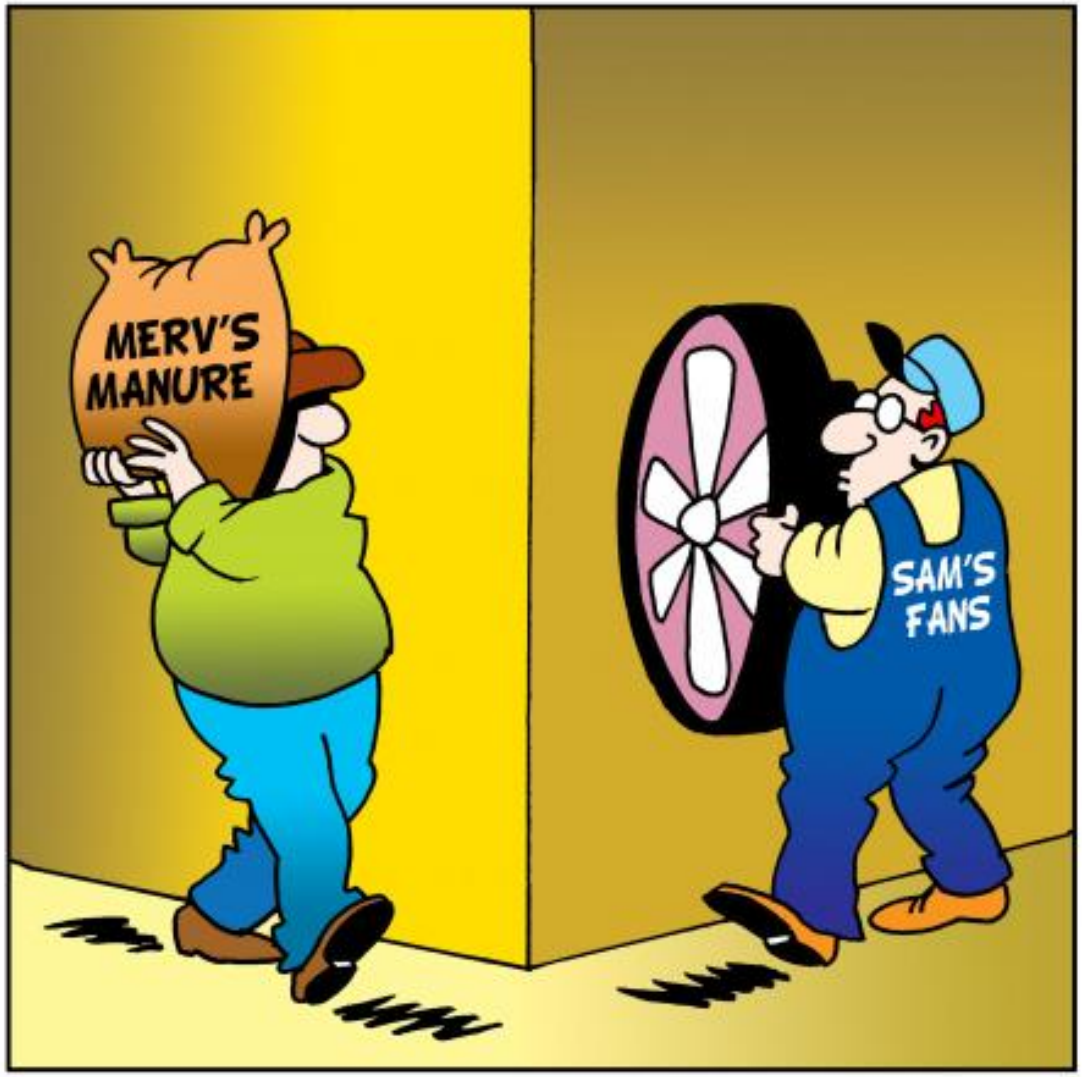
Outcomes

- These conclusions may be used to re-evaluate the criteria required for the pre-market assessment of genetically engineered plants and the foods and feeds derived from genetically engineered plants
- Especially useful for retransformants
  - Retransformants are plants which have been transformed with the identical construct(s) as a previously authorized plant of the same species which confers the same trait
  - Often generated for vegetatively propagated plants
  - Can be resource intensive
- Work is still continuing to determine how best to apply the conclusions of this work and to finalize the paper documenting these findings

Conclusions

- Risk Assessment of GE plants is a fairly new science and we have started with the highest level of precaution
- With nearly 20 years of experience can we re-evaluate some of our early concerns and put them in perspective
- Unintended effects are an outcome of all forms of plant breeding do we have the correct perspective for those arising from genetic engineering
- Canada is embarking on a process to examine some of the consequences of unintended effects and put them into context with conventional breeding
- Over the next 2 days we will be examining unintended effects from a variety of perspectives and try and shed light on the concerns and how best to approach them

Sometimes Unintended Effects Happen

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