New breeding technologies in plant sciences

GPC-SEB workshop, 7-8 July 2017, Gothenburg, Sweden

Historical Evolution of Biosafety Legislation and Key Definitions.

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- 1986 – 2000: responsible for biosafety regulation in the Netherlands
- 2000 – today: assisting governments and international organisations
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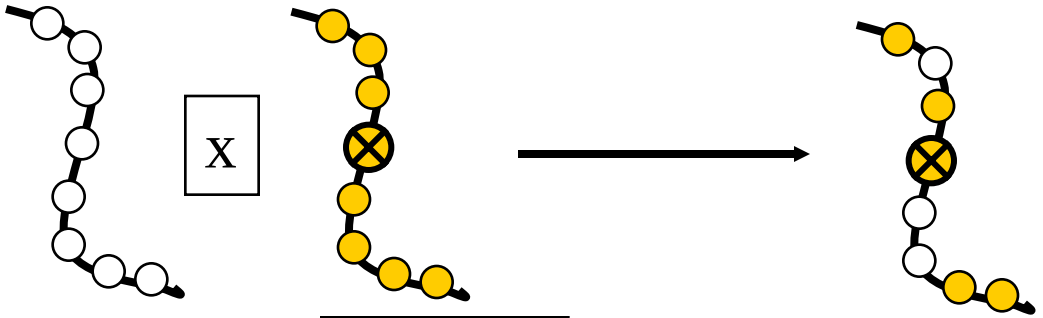
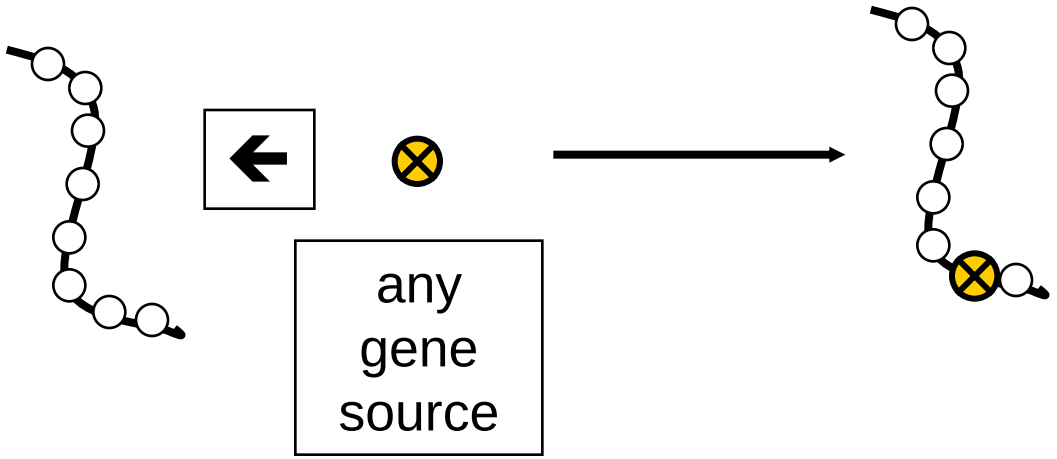
Genetic Modification

Traditional plant breeding



Genetic Modification



Genetic Modification

Technical advantages, e.g.:

- More specific and faster
- Maintaining cultivar characteristics (breeding brings in difficult to remove ‘unwanted’ genes)
- Possible with plants and animals that do not cross sexually
- Tweaking expression (e.g. stress induced, tissue specific)
- Much greater reservoir of genes; in principle any gene from any organism can be introduced in another organism.

Biosafety – Historical highlights

1972: First publications on rDNA

1974: 'Berg Letter' published in *Science*, anticipated benefits and potential risks, calling for a voluntary moratorium.

1975: Asilomar : technique not inherently risky, but potential for novel combinations, safety 'case by case', end of moratorium.

1976: US-NIH Guidelines for rDNA micro-organisms in laboratories

1978: Other countries follow, e.g. UK (1978), Netherlands (1979)

1986: OECD "Blue Book", rDNA safety recommendations; key concepts for risk assessment and risk management

Biosafety Regulations

1986: US coordinated framework for regulation of biotechnology

1990: EU Directives on Contained Use and Release of GMOs

1992: Agenda 21, “maximise benefits, minimize risks”
>>> Convention on Biological Diversity

1996: Canada (CFIA, Health Canada)

2000: Cartagena Protocol on Biosafety - transboundary movement

~ 2000 onwards: Review and revision of regulatory systems (e.g. EU)

~ 2010 onwards: Are organisms developed through NBTs covered by the regulations? Depends on the **definitions**

Definitions - History

1986: OECD “Blue Book”:

Definitions of genetic manipulation and recombinant DNA varies in detail between countries, but rDNA organisms are described as constructed by introducing DNA from a “donor” organism into a “recipient”

E.g.: UK: *formation of new combinations of heritable material by the insertion of nucleic acid molecules, produced outside the cell, via vector system so as to allow their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation.*

Definitions – Historical highlights

Debate as of the mid 80s: which organisms should be subject to prior risk assessment?

Observations put forward:

- Conventional breeding and rDNA can both result in novel genetic combinations that can cause adverse effects
- rDNA techniques themselves do not confer risky characteristics
- rDNA can make a broader range of novel combinations

Options discussed:

- Include all conventionally produced organisms?
- Focus on ‘risky’ organisms?
- Focus on ‘novel’ organisms ?

Which organisms subject to prior risk assessment?

Considerations:

- Include all conventionally produced organisms: is there an unmet need to include them?
- Focus on ‘Risky’ organisms: how to define which are risky?
- Focus on ‘Novel’ organisms: how to define “novel”?
  - Genotypic and/or phenotypic?
  - ‘Does not exist’ or ‘is unlikely to happen’?

>> Different approaches in different systems, most focus on novelty

US Coordinated Regulatory Framework for Biotechnology

- Department of Agriculture (USDA-APHIS-BRS)
  - Plant Protection Act (PPA)

- Environmental Protection Agency (EPA)
  - Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
  - FFDCA: Setting allowable levels of pesticides in food
  - Toxic Substances Control Act (TSCA)

- Food and Drug Administration (FDA)
  - Federal Food, Drug and Cosmetic Act (FFDCA)

Definitions: USA - USDA

USDA Plant Protection Act, Protecting against damage from plant pests and noxious weeds

Regulatory trigger:

- the use of genetic engineering in combination with
- the use of plant pest as recipient, donor or vector, in the transformation process.

Definitions: USA – FDA

FDA: Authority based on Federal Food, Drug and Cosmetic Act (FFDCA)

Guidance in the Federal Register of 1992:

> "The 1992 policy applies to foods developed from new plant varieties, including varieties that are developed using recombinant deoxyribonucleic acid (rDNA) technology (which is often referred to as "genetic engineering" or "biotechnology").
>
> This guidance document refers to foods derived from plant varieties that are developed using rDNA technology as "bioengineered foods."

Definitions: USA – EPA

EPA: authority based on FIFRA, FFDCA, TSCA:

Plant-Incorporated Protectant (PIP, 2001) - a pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for the production of such a pesticidal substance. "

PIPs developed through conventional breeding will remain exempt from all FIFRA and FFDCA requirements, with the exception of adverse effects reporting requirements for manufacturers.

Definitions: EU (1990/2001)

GMO means an organism in which the genetic material has been altered in a way that does not occur naturally;

Annex: Genetic modification occurs at least through the use of:

- rDNA techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation;
- Direct introduction, e.g. macro injection
- fusion techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally.

Definitions – Canada (1996)

CFIA (1996, based on the Seeds Act and Feed Act) and
Health Canada (Food and Drug Act)

Plants with novel traits fall under the regulatory trigger of the seeds regulations if:

- They have a novel trait that was not present prior to December 1996 in germplasm of the same species in Canada, and
- that plant poses an environmental risk.

Definitions – CPB

Cartagena Protocol on Biosafety: (2000)

- "Living modified organism" means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology;

- Modern biotechnology" means the application of:
  - In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or
  - Fusion of cells beyond the taxonomic family,

  that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection;

Definitions - EU

Question whether and to what extent organisms developed through NBTs such as genome editing fall under the definition of GMO.

Discussion: “Altered in a way…that does not occur naturally…?”

Refers to:

- Process/technique ?
- The product/resulting organisms ?
- Both?

Definitions - EU

Legal clues: The law itself, explanatory notes, Jurisprudence, doctrine

The final word is with the European Court of Justice (ECJ).

Interpretation by the ECJ: “the wording, general scheme and spirit”

- *Literal interpretation*, text of the definition and the annexes

When the wording in itself is not conclusive:

- *Systemic interpretation* (general scheme), internal and external consistency (e.g. CPB)
- *Dynamic interpretation*, e.g. teleological or functional, see ERA, pushing an interpretation ‘to its limits’

[See also Callebaut 2015]

Definitions – EU (2001)

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Definitions - EU

My conclusion:

For an organisms to fall under the EU definition of GMO requires
a) the use of certain techniques ('trigger') and
b) a certain level of novelty of the resulting combinations of genetic material.

E.g. small point mutations obtained through genome editing would not result in a GMO.

Definitions - EU

Views of others and other views:

- European Commission:
  - formulating views by taking into account reports of a WGNBT (2012), EFSA, JRC and Legal Services
  - Confirmed in reply to MEPs, both process and product relevant

- D and SE authorities have formally concluded that certain organisms developed through ODM and CRISPR are not GMOs
- D, UK, IRL and ES confirmed in a letter to the EC that the EU GMO definition relies on the technique and the resulting organism.

- Some NGOs adhere to a 'process based' interpretation arguing that "these technologies are considered likely to bring negative impacts on human and/or environmental health".

Future Regulation

Distinguish various categories:

- *Mixing genes between sexually compatible organisms*: cross breeding, hybrids, marker assisted selection, embryo-rescue, polyploidy, cis-genesis,

- *Generating genetic variation within existing genomes*: mutation breeding, genome editing.

- *Generating novel genetic combinations*: e.g. Introducing traits from an unrelated organism into another: genetic modification/genetic engineering.

TACK!