The risk-based case for regulating new molecular breeding techniques

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DRAFT. IN CONFIDENCE

- The biosafety case for mandatory risk management of the new techniques is just as compelling as the trade-related reasons.
- Austrian government agencies are among the few to consider the biosafety risks posed by the new generation of GM methods. Their conclusion, over three separate, high-level reviews of the biosafety risks, is that **new techniques warrant the same regulatory risk assessment as GMOs under current law.** (AGES 2012; 2013; AEA 2014)
- They also specify that **case-by-case assessment** is required due to the diversity of "approach, methodology and unique characteristics" across the different techniques (AEA 2014: 75).
- Biosafety risk arises because:
    - **The techniques are so new** or have only recently been applied to plants and animals to deliver new commercial cultivars or breeds. **There is insufficient biosafety data to inform proper risk assessment or to deem the new techniques 'safe by design'**. Nevertheless, literature to date confirms that unintended or off-target effects are to be expected.
    - **The technological boundaries of new GM techniques are still evolving**. As such, they have the potential to cause greater degrees of genetic change than is currently described in standard profiles.
    - **Combined use of the new techniques will further expand the scope and nature of biological change that results**. As yet, there is little or no biosafety research on plants or animals produced using combinations of the new techniques, when such combinations are expected to be routine.
    - **There is very little data, and the data that is available is not evenly distributed across all types of organisms**. Thus, the potential adverse effects are highly unpredictable, especially for microbes and animals.

  The reports indicate that some techniques may not require the same degree of routine risk assessment. However, at this early stage in their development, an adaptive risk management approach is recommended, whereby the new techniques are subject to mandatory risk assessment and risk management until such time as independent biosafety data supports either lesser regulatory requirements or deregulation.

EXCERPTS FROM THE REPORTS

Insufficient biosafety data on new GM techniques

- "uncertainties associated with potential risk issues are far from being resolved […] due to the quite limited availability of relevant scientific data" (AEA 2014: 73)
- "For the majority of the new techniques, no concrete data is available on the biosafety of the new phenotypes." (Vogel 2012: 88)
- "insufficient knowledge is available as regards their potential for adverse effects." (AEA 2014: 76)

Same risk assessment requirements as for GM

- The necessary response to "the current situation of insufficient knowledge" is to **"apply[] requirements to identify and assess such uncertainties similar as for GM plants"** (AGES 2012: 6)
- "biosafety considerations conducted for NPBT [New Plant Breeding Techniques] crops have indicated that the general approach developed for **the risk assessment of GM crops in principle would also be appropriate to address the currently identified risk issues for NPBT-crops**.' (AEA 2014: 76)
- "**the basic principles implemented in relevant biosafety regulation frameworks** – European legislation, Cartagena Protocol, Canadian 'Plants with Novel Traits' regulation **- are considered to be appropriate** for NPBT-crops" (AEA 2014: 76)
- "for all new plant breeding techniques **core elements of the current risk assessment requirements for GM plants are mandatory**". (AGES 2013: 5)

Unintended effects

- "Scientific publications indicate that neither the efficiency nor the specificity of the technologies aiming at targeted alterations of plant genomes can be controlled sufficiently. **Unintended effects cannot be excluded."** (AGES 2012: 135)
- **"Indirect and delayed effects may also result from unintended effects** of modifications by NPBTs or result from stability issues of the modifications and traits in NPBT crops" (AEA 2014: 74)
- For that reason, "**the molecular characterization has to be as substantial as for transgenic plants" (AGES 2012: 135)**

Indistinct technological boundaries

- As noted , the potential of the new GM techniques to change an organism may be far greater than the 'thumbnail' profiles that are routinely used to describe them. By way of example, oligonucleotide-directed techniques (such as so-called oligonucleotide-directed mutagenesis) are often portrayed as a relatively discrete intervention.

However, it is technologically feasible to repeatedly use the technique to "change the sequence of a gene" or to "introduce the promoter in front of a genomic sequence that was previously not expressed". That is, "a successive cycle of directed mutagenesis could introduce an entirely new sequence." (COGEM 2010)

- The Austrian Environment Agency reports that the new techniques will "mostly be used in combination" with one another, as well as with GM and conventional breeding approaches. (AEA 2013: 75). Some of the possible combinations have been identified in reports to the Swiss and Austrian governments (Vogel 2012; AGES 2012; 2013)
- Combinations of the new techniques may also determine the scope of change that can be achieved, and the overall risk profile. but as yet there has been no or little assessment of the biosafety implications of combining the techniques.
- However, by way of example, the combination of certain techniques – such as ZFN-3 and cisgenics – may be used deliberately in an attempt to hamper detection of the cisgenic modification (AGES 2012: 134) and thus make risk management more difficult.

Possible Combinations of New GM Techniques
(Translated and adapted from Vogel 2012: 77)

Technique	Theoretically combinable with
Agroinfiltration	Accelerated breeding; reverse breeding, RNA-dependent DNA methylation
Accelerated breeding	Grafting; virus-induced gene silencing; virus-supported gene expression
Cisgenesis	Meganuclease-, TALEN- and zinc finger nuclease- techniques; grafting
Induced hypomethylation	Virus-induced gene silencing
Intragenesis	Meganuclease-, TALEN- and zinc finger nuclease- techniques; grafting
Meganuclease techniques	Cisgenesis; intragenesis; virus-supported gene expression
Methyl transferase techniques	virus-supported gene expression
Grafting on GM rootstock	Accelerated breeding; cisgenesis; intragenesis; reverse breeding; RNA-dependent DNA methylation
Reverse breeding	Grafting; virus-induced gene silencing; centromere-mediated genome elimination
RNA-dependent DNA methylation	Grafting; virus-induced gene silencing
TALEN	Cisgenesis; intragenesis; virus-supported gene expression
Transformation with wild-type agrobacteria	Grafting
Virus-induced gene silencing	Accelerated Breeding; reverse breeding; RNA-dependent DNA methylation
Virus-supported gene expression	Accelerated breeding; meganuclease-, TALEN- and zinc finger nuclease techniques
Centromere-mediated genome eliminiation	Reverse breeding
Zinc finger nuclease	Agro-infiltration, cisgenesis, intragenesis, virus-supported gene expression

Deregulating the new techniques would increase biosafety risk

- It would drive technology selection to new, unregulated techniques over regulated approaches, at a time when their risk profile is still emerging.
- The incentive to undertake biosafety research is effectively extinguished, thus prolonging ignorance or uncertainty. Further, independent safety testing standards and requirements - typically established by regulation - are also unlikely to be forthcoming in the absence of a legal requirement to conduct biosafety research according to independently agreed standards.
- Detecting products of some of the new techniques will be difficult without regulatory requirements that ensure that relevant information is in the public domain.

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