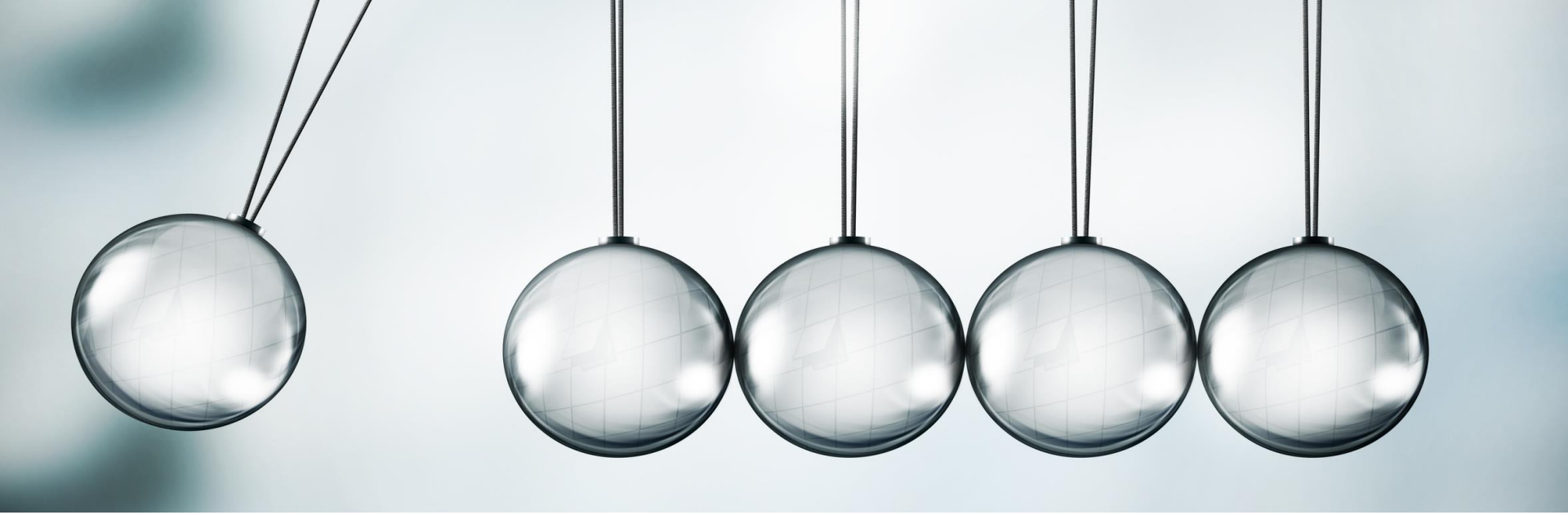
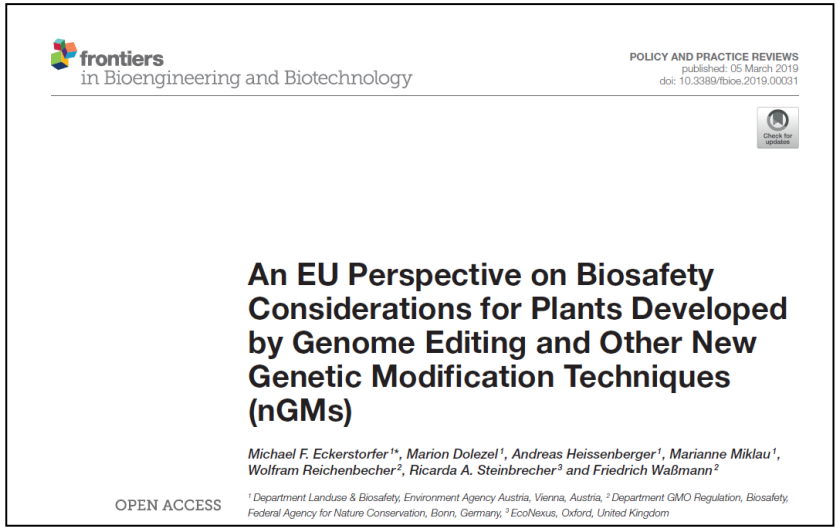


# BIOSAFETY OF GENOME-EDITED PLANTS: CHALLENGES FOR THE RISK ASSESSMENT

MICHAEL ECKERSTORFER

PERSPEKTIVEN FÜR UMWELT & GESELLSCHAFT umweltbundesamt



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POLICY AND PRACTICE REVIEWS
published: 05 March 2019
doi: 10.3389/fbioe.2019.00031

An EU Perspective on Biosafety Considerations for Plants Developed by Genome Editing and Other New Genetic Modification Techniques (nGMs)

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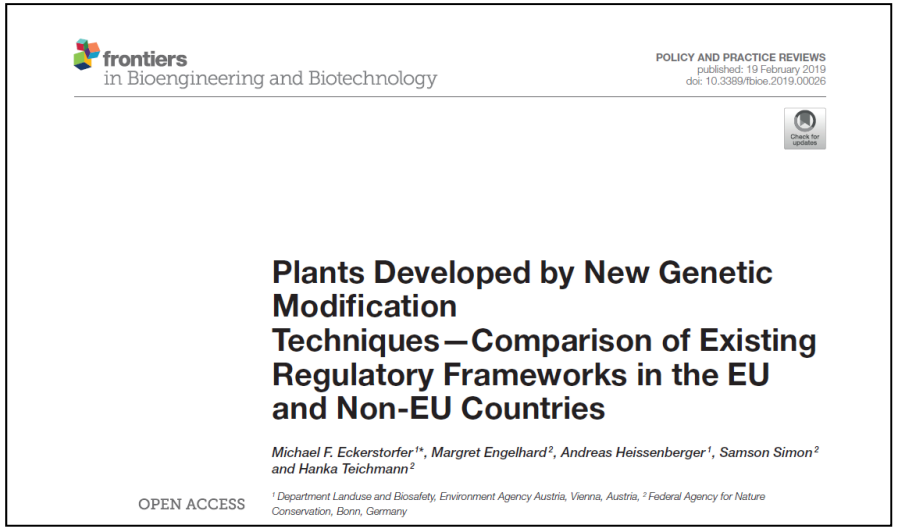

frontiers in Bioengineering and Biotechnology

POLICY AND PRACTICE REVIEWS
published: 19 February 2019
doi: 10.3389/fbioe.2019.00026

Plants Developed by New Genetic Modification Techniques—Comparison of Existing Regulatory Frameworks in the EU and Non-EU Countries

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**Kind thanks** for

- Invitation to this event
- Financial support: German Federal Agency for Nature Conversation (BfN), Research & Development Grant No. 3516890400 (FKZ)



PERSPEKTIVEN FÜR UMWELT & GESELLSCHAFT umweltbundesamt

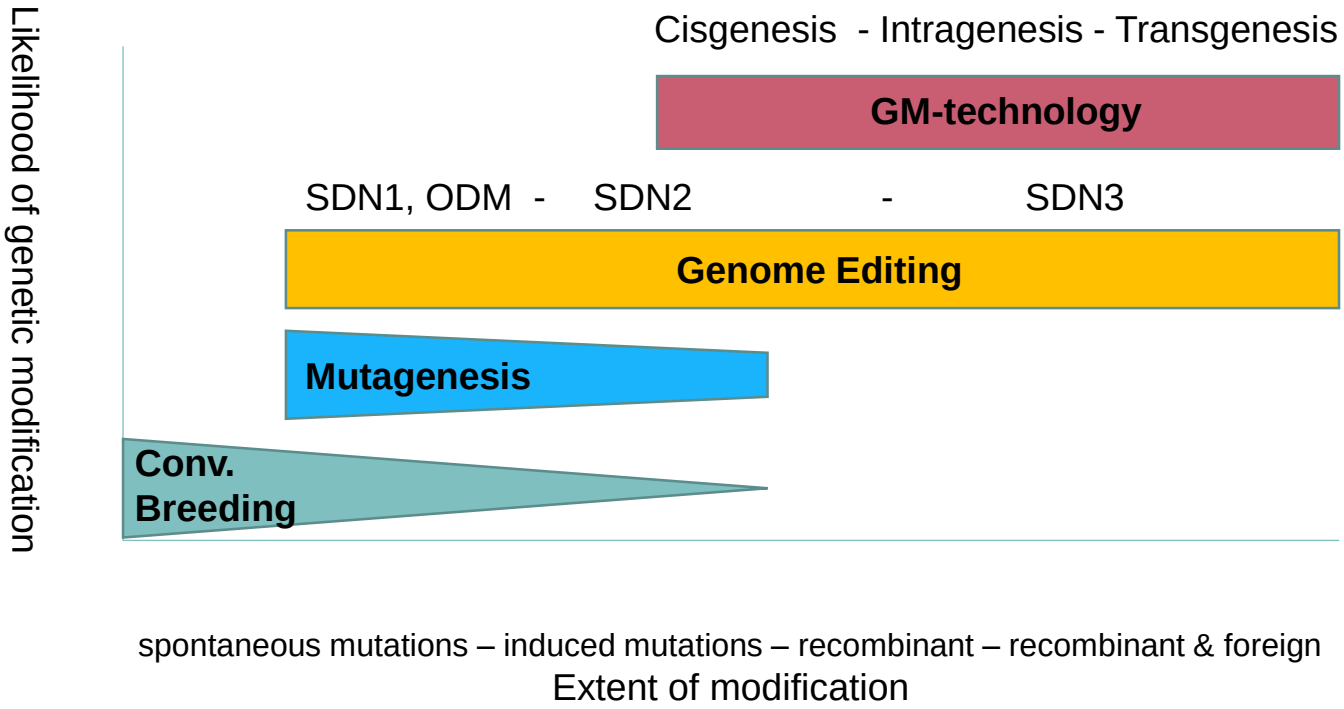
# OVERALL CHALLENGES concerning GENOME EDITING

- Scope of Techniques and Terminology
- **Biosafety issues**
  - **Intended / unintended effects on health & environment**
- Regulatory issues
  - Coverage by existing regulatory frameworks for GMOs (Regulatory trigger)
  - Future regulatory development (amendments existing regulations / new regulations)
- Enforcement issues
  - Detection and identification supporting traceability & labeling
- Sustainability issues
  - Socioeconomic considerations
  - Agroecological considerations and policies (Innovations for a sustainable agriculture)

# MATTERS WHICH COMPLICATE THE DEBATE

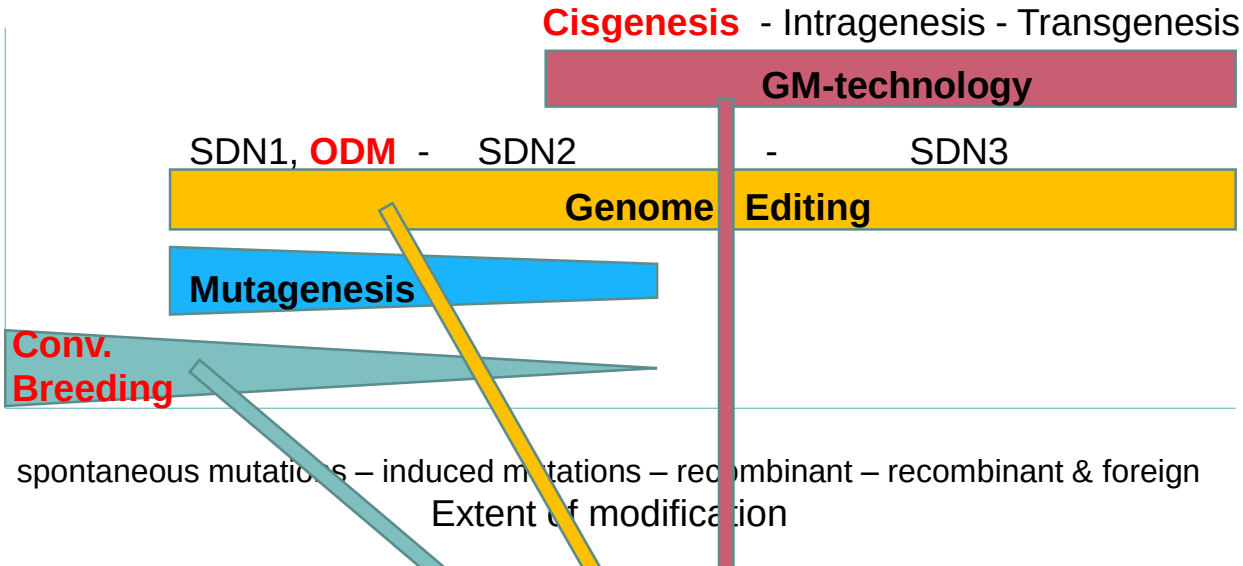
- Limited ability to differentiate New Biotechniques and Conventional Breeding approaches
  - GM-Technology, Genome editing, other new techniques vs. Breeding based on mutagenesis /selection
- Wide range of Genome Editing approaches and techniques
  - SDN1, SDN2, SDN3, ODM, base/prime editing, epigenetic engineering
- Different depth of intervention and specificity of editing
  - Knockout vs. Functional modification of genes
  - Single vs. multi-allelic or multi-gene modification (multiplexing)
- Wide range of traits under development
  - Novel vs. non-novel traits
- Shortcomings of the current risk assessment process
  - Assessment of trait- and method-related unintended effects

# SHADES OF GREY rather than BLACK & WHITE



# DIFFERENT TECHNOLOGY – SIMILAR OUTCOMES

## (ALS herbicide-resistant crop plants)




# GENERAL ISSUES concerning RISK ASSESSMENT

- Are there general denominators for risk/safety ?
  - i.e. indicators for more or less risky applications?
- How to devise a regulatory approach to include all applications, which should be risk assessed?
  - Regulatory scope, triggers and exemptiions
- How to focus risk assessment?
  - What are relevant case-specific issues for assessment?
  - Flexibility of the design for risk assessment
- Is the existing guidance for risk assessment sufficient?
  - General principles and risk areas?
  - Specific guidance sufficient?

# (UN-)SUITABLE DENOMINATORS OF RISK/SAFETY

- Type of Genome Editing? (SDN1 - SDN2/ODM – SDN3)
  - NOT APPROPIATE (just easier to implement by legislation)
- Size of genetic changes? (Length of modified sequence)
  - NOT APPROPIATE (however predictive of ability to identify products)
- Precision of editing? (Specificity for particular target sites)
  - **RELEVANT** for UNINTENDED (off-target) EFFECTS (e.g. intentional „dirty“ editing )
- Complexity of intervention? (Depth of intervention)
  - **RELEVANT** UNSPECIFIC INDICATOR (complex genetic changes, complex physiological/penotypic changes)
- Novelty of trait?
  - **RELEVANT** for EFFECTS by INTENDED CHANGES (level of familiarity)
- Speed of development?
  - **RELEVANT** UNSPECIFIC INDICATOR (length of observational period)

# RISK ASSESSMENT CONSIDERATIONS (SAM 2017)

- Effects due to **intended changes** present in the modified plant
  - Trait related effects:
    Herbicide resistance, disease resistance (viral, bacterial, fungal), compositional changes,
    enhanced fitness against environmental stressors, alteration of morphological or reproductive plant characteristics
- Effects due to **unintended changes** present in the modified plant
  - Method related effects:
    e.g. due to transformation (GM tools), nGM mechanism (off-target effects),
    other biotechnological methods (in vitro cultivation, regeneration)
- Effects due to **characteristics of the modified plant species** and its **interaction with the receiving environment**
  - (Major) crop species, other agricultural and ornamental plants, (fruit) trees
- Effects due to the **intended use of the modified plant**

# TRAIT-RELATED CONSIDERATIONS

- **Herbicide resistance (HR) against broadband herbicides**
  - ALS-Inhibitors (OSR, potato, rice, maize, soy, tobacco), glyphosate (strawberries, flax, cassava, cotton), glufosinate, bialophos, 2,4-D (maize, tobacco)
- **Disease resistance against plant pathogens**
  - Bacterial and fungal pathogens (grapefruit, wheat, tomato, grapevine, apple, and rice)
  - Viral pathogens (cucumber)
- **Compositional changes**
  - sugar and starch content (potato and rice), lipid composition (*Camelina* and soybean), lignin (sugarcane), fragrance (rice)
- **Enhanced fitness** (environmental stress), **morphological or reproductive characteristics**
  - Abiotic stress response (cold, drought, salinity)
  - Increased seed shatter resistance (oilseed rape), early maturation and facultative parthenocarpy (tomato), early flowering, larger fruit and more flower buds (tomato), *de novo* domestication (tomato)

| Trait | Potential adverse effects | Comp. issues |
|---|---|---|
| **Herbicide resistance (HR) (broadband herbicides)** | Impacts on biodiversity due to herbicide use | GM |
| | Development of HR-weeds (selection, gene flow) | GM |
| | HR-volunteer plants in subsequent crops | GM |
| | Herbicide cocktail effects (residues, metabolites) | GM (stacks) |
| | Pleiotropic effects of overexpressed HR-genes | |
| **Disease resistance (viral, bacterial, fungal pathogens)** | Pleiotropic effects on plant development (e.g. multiple mlo-knockouts) | GM (RNAi) |
| | Evolution of pathogens (selection of resistant pathogens, secondary pathogens) | GM (IR) |
| | Effects on (soil) non-target organisms (antitimicrobials) | GM |
| **Compositional changes** | Animal and human health effects (nutritional effects, toxicity, allergenicity) | GM |
| | Environmental effects due to changed composition (herbivore attractivity, NTOs, decomposition) | GM |
| | Environmental effects of morphological changes (stability) | GM |
| **Altered env. fitness, morphology / reproduction** | Increased invasiveness of modified plant | GM |
| | Negative effects on protected relatives (gene flow) | GM |
| | Increased fitness of weedy relatives (gene flow) | GM |
| | Unintended effects of *de novo* domesticated plants (nutritional) | |

# TRAIT-RELATED CONSIDERATIONS - ISSUES

- Limited knowledge and familiarity (no history of safe use)
  - Novel crops / agricultural plants (new species, wildforms)
  - Novel traits (phenotypes)
  - Changed agricultural management
- Unintended effects associated with intended changes
  - Pleiotropic effects
  - Unintended effects in non-transgenic plant parts (transgrafting)
  - Complex physiological effects of multiple changes (multiplexed Genome Editing)
  - Complex regulatory effects on morphology, development and reproduction

# CASE-SPECIFIC framing of the RISK ASSESSMENT

## Different categories of applications

- Genome-edited plants with traits and usage known from conventional approaches
  - Familiarity concerning effects upon use should be considered during assessment
- Genome-edited plants with traits similar to existing GM plants and associated with comparable risk issues
  - e.g. herbicide resistance or disease resistance, compositional changes
  - previous experience with the risk assessment of comparable GMOs should be taken into account
- Genome-edited plants with traits which have not yet been established and thus are novel
  - Similar approaches for risk assessment as implemented for GMOs should be applied

# METHOD-RELATED CONSIDERATIONS

- Holistic assessment of unintended changes is required
  - Typically a combination of different methods is used
  - Unintended changes due to transformation procedures (GM methods, introduction of editing components)
  - Unintended changes due to integration of unwanted genetic material (method-related components)
  - Off-target effects genome editing (SDNs, ODM) (unintended as well as “intended” off-target effects)
  - Unintended changes due to other required biotechnological methods (*in vitro* cultivation, protoplast technology, regeneration)
- Unintended changes at genomic locations other than the genomic target site(s)
  - Modifications usually not genetically linked to the desired trait(s)
- Unintended molecular changes in the vicinity of the intended site of modification
  - Different from the intended modifications, but tightly linked to the desired trait(s)

# RELEVANT ISSUES FOR RISK ASSESSMENT

- Combination of biotechnological and conventional methods
  - Genome Editing, GM technology & other biotechnological methods
- Precision (specificity of genome edits)
  - Potential to introduce off-target changes
  - Predictability of off-target changes
- Depth of Intervention
  - Single vs. multiple changes (multiplexed, serial changes)
  - Physiological effects of modified targets (specific vs. pleiotropic effects)
- Impact on time of development (observation)
  - Direct modification of elite lines, plants that are propagated vegetatively
  - Modification of plants with long generation cycles (trees)

# CASE-SPECIFIC approach to the RISK ASSESSMENT

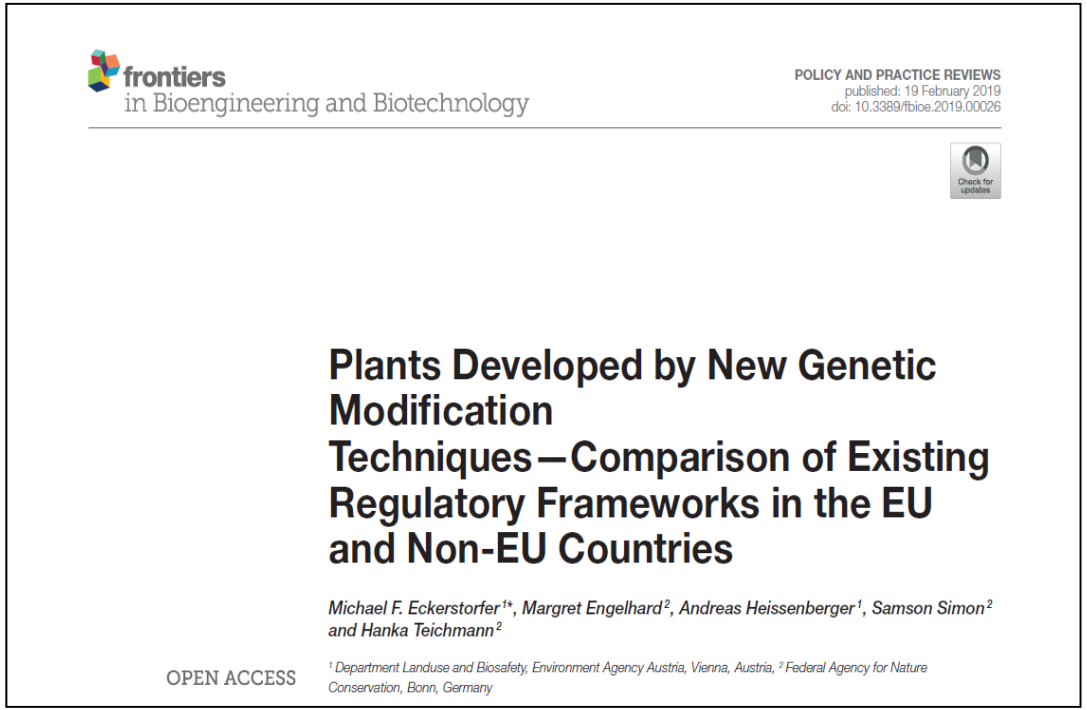
- Case-specific risk assessment requirements
  - the nature of the developed trait,
  - unintended consequences of the modification introduced,
  - the available experience with comparable products (familiarity), and
  - relevant protection goals specified by the respective countries.

- Appropriate molecular characterization to assess
  - the unintentional presence of any transgenic inserts in the final product, and
  - the presence of off-target modifications and other unintended genetic changes, which might result in adverse phenotypic effects.

- Phenotypic characterization
  - to specifically test parameters related to risk issues associated with a particular genome-edited plant

# CONCLUSIONS FOR RISK ASSESSMENT

- Wide range of methods and traits need to be considered
- No safety by default
  - The issue that certain changes could (hypothetically) be developed with conventional methods (or spontaneous mutation) is not indicative of product-safety
  - Small size genetic changes are not indicative of (environmental) safety
  - High precision of modification is not indicative of the safety of trait(s)
- Limited knowledge for assessment available
  - Novel traits and complex traits (Non-trivial physiological / phenotypical effects)
  - Limited predictability of (unintended) changes and effects
- Increased speed of development needs to be considered
  - Impacts observation and elimination of unintended changes



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POLICY AND PRACTICE REVIEWS
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Check for updates

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- Comparison of existing regulatory frameworks
  - Similarities & differences
- (Possible) regulatory approaches
  - Options for regulation of nGM products

# LIMPING ALONG AND LAGGING BEHIND: REGULATION

- Risks not correlated with specific types of techniques (e.g. SDN-1, SDN-2, ODM, SDN-3)
  - Rather with traits and characteristics of approach (complex, deep, fast, dirty)
  - Challenges for devising an appropriate regulatory approach (trait/method related criteria)

- Existing regulatory frameworks are not consistently addressing New Techniques
  - Particularly they fail to consistently address the level of risk associated with different applications
  - Neither are proposed/implemented amendments increasing consistency

- Broad but flexible regulatory framework probably best to address biosafety issues
  - Exclusion from biosafety regulation is not a good option – other applicable regulation is not well suited to address biosafety issues
  - General principles of GMO regulation frameworks are suitable
  - Case-specific „outcome-based“ assessment strategies need to be developed

# THANK YOU FOR YOUR ATTENTION!

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