Regulatory and societal considerations of new genetic techniques

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Member GMO panels
Norwegian Scientific Committee for Food Safety (VKM), Oslo (2007-)
European Food Safety Authority (EFSA), Parma (2009-2015)
- Guidance on GM animals (2013)

*Present personal view

“Old” techniques

GM-plants

- Commodity crop plants
  - Stacked pesticide and herbicide traits

GM-animals/insects

- Growth enhanced fish
- Insect population control
  - Mosquitos, agricultural pests

GM-microorganisms

- Contained use

Recombinant DNA - transgenic
Random insertions of unrelated DNA
Regulatory framework

New techniques

"Old"

Genetically modified organisms (GMOs)

Recombinant DNA - transgenic

- Random insertions of unrelated DNA
- Regulation, labeling

"New"

Genome edited or base edited organisms

Recombinant DNA?

- Site specific changes of the genome
- Unclear/resolved regulatory status

New techniques / approaches

- Site-directed nucleases
- Gene drive systems

- Intragenesis and cisgenesis
- Para-transgenesis
- RNA interference

JRC, 2011, http://ftp.jrc.es/EURdoc/JRC63971.pdf

EFSA, 2012, http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2943/epdf

EFSA 2012. Scientific opinion addressing the safety assessment of plants developed through cisgenesis and intragenesis, EFSA J. 10(2):2561

Site-directed nucleases (SDNs)

Genome or base editing

CRISPR-CAS, Talen, ZFN

Enzymes that generate site-specific breaks in the genome

- Targeted modifications at particular sites
- Insertions, deletions or base changes
- Minor or no GM seq. in final product

CRISPR-CAS

- Prokaryotic immune system - adopted for engineering
- CAS9 protein and single guide RNA (sgRNA)
- Modified CAS proteins allows for single strand breaks

Site-directed nucleases (SDNs)

DNA repair of the breaks produce desired genetic changes

- Protein guided target site recognition
  - Zink fingers, Talen

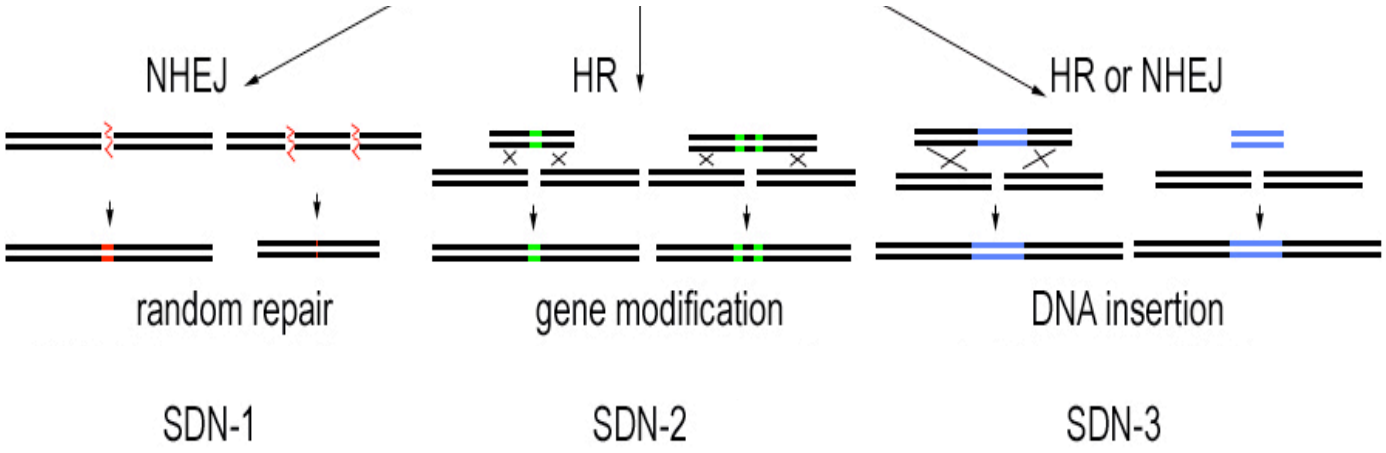
- RNA guided target site recognition
  - **CRISPR-CAS9**

- Take place with or without provided DNA templates
- Specificity and cleavage at non-targeted locations?

Site-directed nucleases

Repair of double strand breaks (DSB) in the genome

- Non-homologous end joining (NHEJ)
- Homologous recombination (HR) (DNA templates)

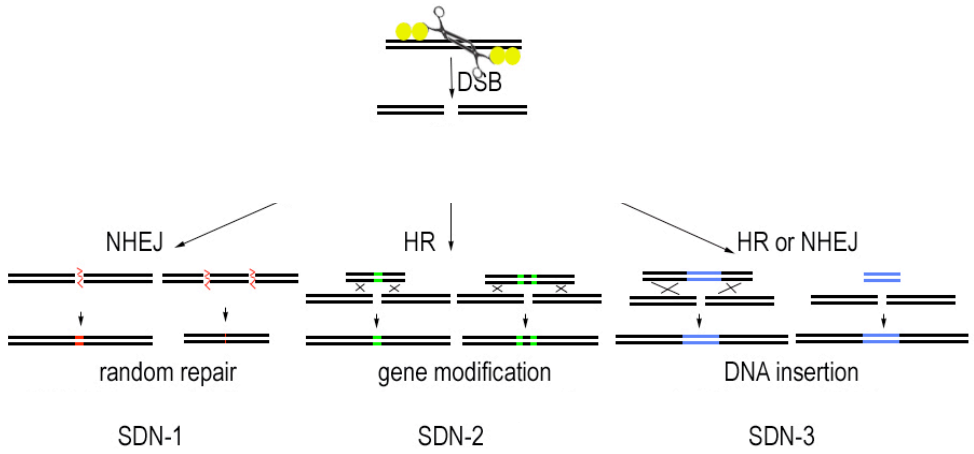


EFSA, 2012, http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2943/epdf

Site-directed nucleases

3 classes of SDN based modifications (EFSA, 2012)

- **SDN-1**: site-specific random mutations or short deletions
- **SDN-2**: a homologous DNA fragment is provided to induce specific minor nucleotide changes (HR)
- **SDN-3**: a provided DNA fragment is integrated via NHEJ or HR



Regulatory implications

SDN = genetic engineering or editing?

SDN the basis for a range of genetic modifications

Targeted single nucleotide changes

- SDN-1
- ss base edits

Introduce specific genetic DNA fragments (small-large)

- Minor nucleotide changes (SDN-2)
- Transgenesis (SDN-3) with DNA from any source
- CRISPR based gene drives (SDN-3)

SDN - process-based considerations

- Recombined DNA sources from multiple species
- Co-integration of vector sequences
- Random breaks and insertion(s) of vector residues
- Local and global genome rearrangements
- New ORF at insertion sides
- Variable expression of traits (original source and new host)
- History of safe use? – organism and introduced traits

Regulation

Targeted modifications reduce overall uncertainty

- Predictability and consistency
  - sub-categorization?
- Harmonized regulation across countries?
- Detection possible?

SDNs

Remaining challenges

- Proven precise site-specific modification
- Knowledge of optimal insertion sites in genomes
- Predictability of trait effects and stabilty of new phenotypes
- Effects of host phenotype

Regulation:

- Currently case-by-case approach
- Not fully developed-harmonized
- Most current CRISPR applications = fall under GM regulation

- EFSA guidance, 2012, 2013, SDN and GM animals

http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2943/epdf
http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2013.3200/epdf

Two types of GMO regulatory frameworks

Process-based

- Focus on the techniques used to produce the GMO
- Techniques used trigger regulations (exemptions)
  - E.g. Argentina, Brazil and the EU

Product-based

- Focus on the risks of new products and novel traits rather than the method of production
  - E.g. Canada

Cartagena protocol on biosafety (CBD), Codex alimentarius guidance

New continuum challenge current frameworks

Gene drives: from unintentional to intentional spread

Current GMO

- Domesticated species
- Limited unintentional gene transfer
- Controlled sexual reproduction
  - Terminator technology, SIT
  - Contamination/hybridization

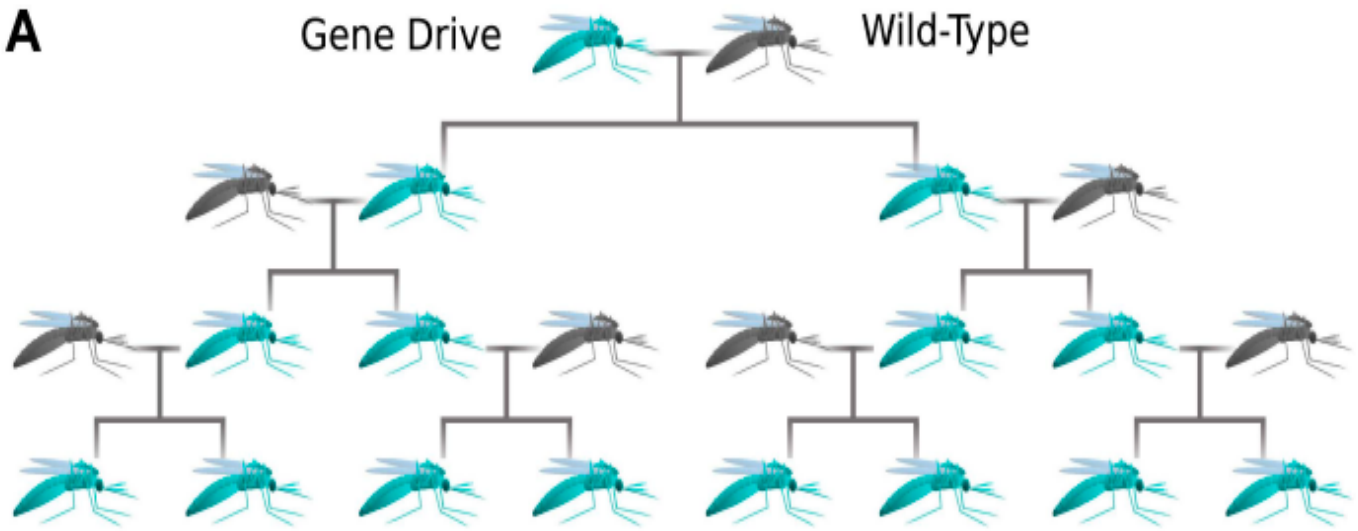
Gene drive systems

- Intentional spread of genes in wild population
- Sexual reproduction
- Structure, migration, and time

Gene drive systems

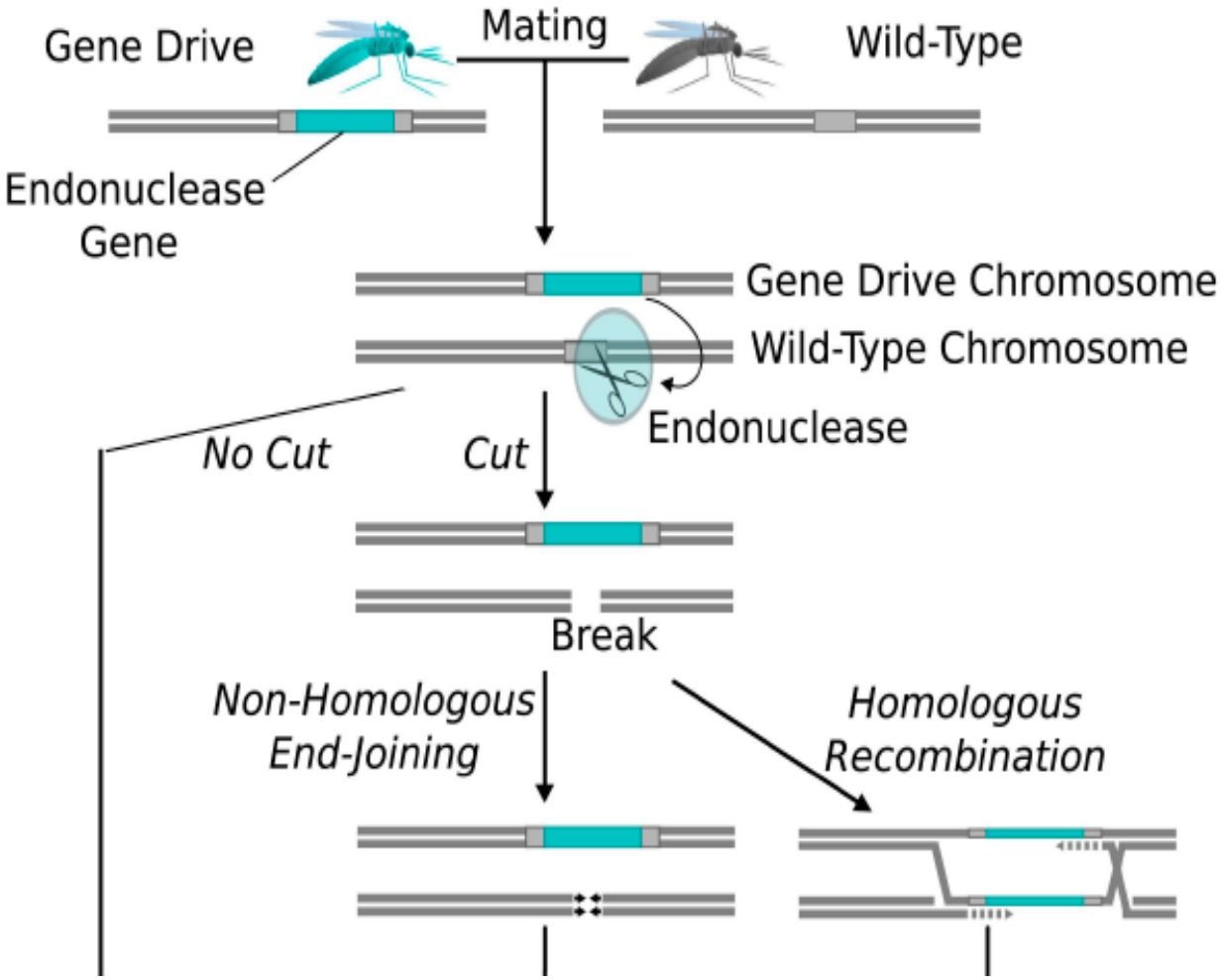
Enhanced inheritance of a genetic element

- Increase of a specific genotype from one generation to the next
- Target populations
- CRISPR-based (RNA guided)



Esvelt *et al.* eLife 2014;3:e03401. DOI: 10.7554/eLife.03401

Gene drive



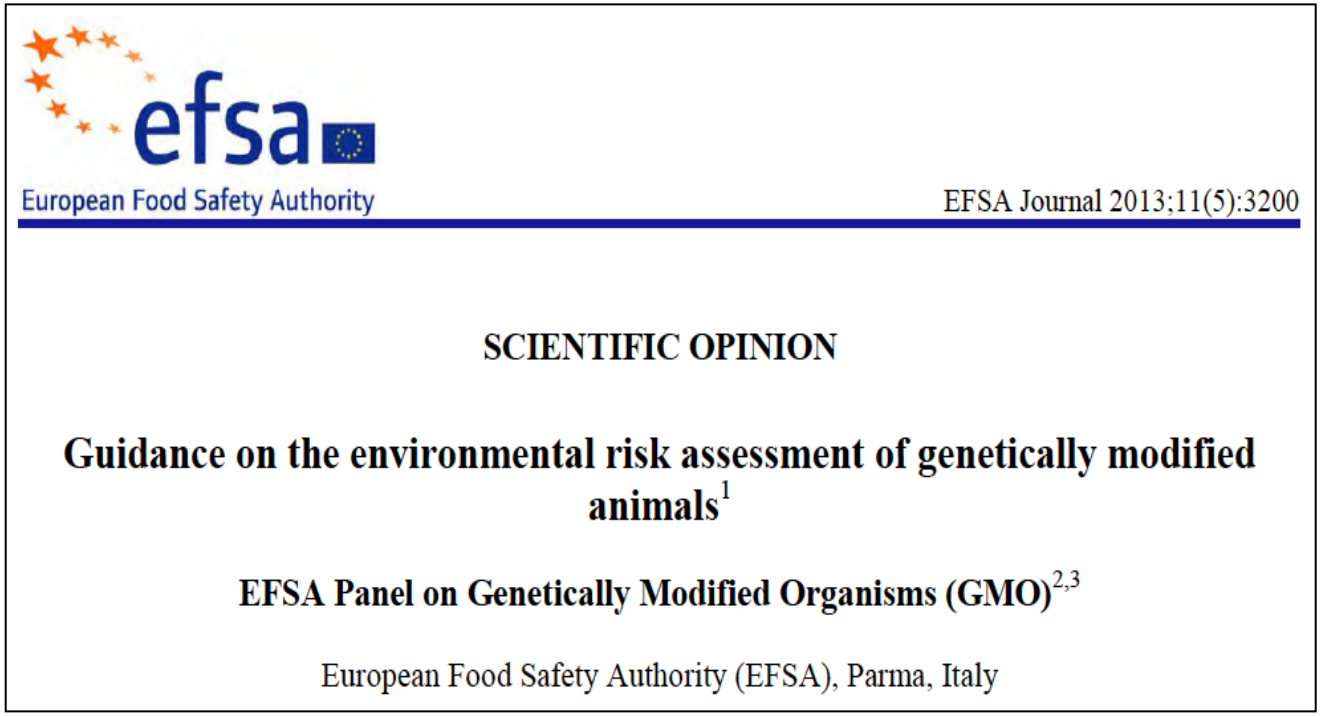
Esvelt *et al.* eLife 2014;3:e03401. DOI: 10.7554/eLife.03401

Gene drive - considerations

- Robustness
  - Proof of concept, species dependence, stability
- Data production for risk assessment
  - Trait, population, interactions, ecosystems
  - Migration
- Public engagement
  - Social context - appraisal - uptake
  - Best practice?
- Regulatory authority and framework
  - International (Cartagena protocol)
  - Step by step, case by case

Gene drive - risk assessment

- Comparator
- Data available – extrapolation
- Different environmental conditions
- Tempospatial
- Uncertainty



efsa
European Food Safety Authority

EFSA Journal 2013;11(5):3200

SCIENTIFIC OPINION

Guidance on the environmental risk assessment of genetically modified animals[1]

EFSA Panel on Genetically Modified Organisms (GMO)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

Gene drive

NAS (2016)

“There is insufficient evidence available at this time to support the release of gene-drive modified organisms into the environment. However, the potential of gene drives for basic and applied research are significant and justify proceeding with laboratory research and highly controlled field trials” .

Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. Washington, DC: The National Academies Press. (2016)

https://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and

New technologies - societal context

- Direct health and environmental concerns
- Data production systems
- Scientific uncertainty, knowledge gaps, standards
- Exposure / cost-benefits
- Public engagement, affected communities
- Expert cultures, consensus – valid concerns (framing)
- Communication and opinion
- Harmonization (regulation)

Values, ethics, cultures

Summary

- New continuum in product categories
- Regulatory authority and framework not yet in place
  - Harmonization – trade
- Area wide data generation
  - Wild populations are poorly understood
  - Population genetics, ecosystems
- Public engagement is key
  - Technology choices reflect values, ethics, priorities, culture
  - Technology availability versus adoption models
  - Uncertainty - trust - transparency

Thank you!

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