A Framework for the Risk Assessment and Management of Gene Drive Technology in Contained Use

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What is a Gene Drive?

Gene drives or ‘selfish genetic elements’ are well known from nature: They do not inherit according to Mendelian law, but increase in frequency with each generation without conferring a fitness advantage.

CRISPR/Cas9 enables construction of a synthetic gene drive, resulting in a GMO
Concerns of Gene Drive Technology

Due to a potential rapid and permanent spread of a gene drive there are concerns that:

- an unintentional release or when kept under a containment not stringent enough may result in an increased spread of the genetic trait into a wild population, with ecological consequences,
- the modified individuals/population can spread beyond national borders.

-> Adequate method for risk assessment is highly needed
Research questions

- How to address the specific features of a gene drive (i.e. increased spread of a genetic trait) in the risk assessment?

- What containment measures are necessary, recognizing the increased risk of spread of the gene drive upon unintentional release?

Starting point:
Risk assessment method according to EU directive 2009/41/EC regulating the contained use of GGM’s.

Risk assessment according to Dir. 2009/41/EC (annex III)

1. Identification of the potential adverse effects on human, animal and plant health and the environment
2. Estimation of the severity of the adverse effects subject to the GMO’s characteristics
3. Estimation of the likelihood of occurrence of the adverse effects subject to the GMO’s characteristics, the environment, and the activity
4. Assignment of a risk class to the activity
5. Implementation of recommended containment level to minimise the risk to the environment
Potential adverse effects of a GDO*

Potential adverse effects which may occur upon an unintentional release:

- **Survival** of the GDO in the environment
- **Genetic transfer** of the gene drive elements to wild relatives

*GDO = 'gene drive organism' = genetically modified organism carrying a CRISPR based gene drive

Severity of the potential adverse effects

Severity is estimated by:

- **Biological characteristics of the organism**  
  e.g. flying / non-flying, ability to survive outside containment, etc.

- **Molecular construction of gene drive**  
  e.g. split gene drive, daisy gene drive, harmful cargo gene

Severity is estimated from negligible – low – medium - high
Likelihood that potential adverse effects occur

Likelihood is estimated by:

- the characteristics of the intended activity
e.g. handling mobile organisms vs immobilized organisms, etc.

- the potentially exposed environment
e.g. climate conditions, presence of mating partners, prevalence of the GD target site in the local population, etc.

Likelihood is estimated from negligible – low – medium - high

Assigning risk classes for activities with a GDO

By combining the estimated levels of severity and likelihood risk classes for a GDO are proposed:

Three risk classes 1, 2 and 3
Defining risk classes for a GDO activity

**Risk class 1: negligible to low risk**
GDO comprises a similar risk as the corresponding GMO, i.e. there is no increased spread of the GDO or its genetic trait in case of unintentional release.

**Risk class 2: medium risk**
A non-permanent impact on the environment, i.e. the spread of the GDO or its trait is transient and the initial situation can be restored.

**Risk class 3: high risk**
A permanent and non-reversible impact on the environment.

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Risk Classes and Risk Management

The outcome of the risk assessment is the assignment of a risk class for which proportionate control measures apply.

Risk class 1: control measures BSL-1 / ACL-2

Risk class 2: control measures BSL-2/3 / ACL-3

(measures to prevent potential adverse effects due to pathogenicity can be omitted)
## Risk Management – Minimal Control Measures

<table>
<thead>
<tr>
<th>Physical requirements</th>
<th>Risk class 1</th>
<th>Risk class 2</th>
<th>Risk class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two layers of physical containment: (1) species appropriate container (unbreakable, escape-proof), and (2) laboratory to include species-specific barriers</td>
<td>Additional layer of physical containment to enclose the species appropriate container</td>
<td>Two door system with interlock</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Work practice</th>
<th>Risk class 1</th>
<th>Risk class 2</th>
<th>Risk class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to all areas used for GDO activities limited to trained personnel and instructed service personnel</td>
<td>Access to all areas used for GDO activities restricted to trained personnel and accompanied service personnel</td>
<td>Monitoring plan available to test for the presence of the gene drive element(s) in the environment in case of unintentional release</td>
<td></td>
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<tr>
<th>Monitoring plan</th>
<th>Risk class 3</th>
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<tbody>
<tr>
<td>Emergency plan prepared in case of detection of gene drive element in the environment</td>
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### Additional control measures are specified for:
- yeast, fungi
- arthropods
- rodents

## Conclusions

Based on the risk assessment method from the CU directive 2009/41/EC:
- Proposal for a structured risk assessment method for GDOs in contained use
- The outcome presents risk classes for GDOs and respective control measures (risk management).

By working with several EU risk assessors together a first step in streamlining the risk assessment method is set.
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