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Experiences with gene drives and risk assessment implications Opinion of the Netherlands Commission on Genetic Modification (COGEM)

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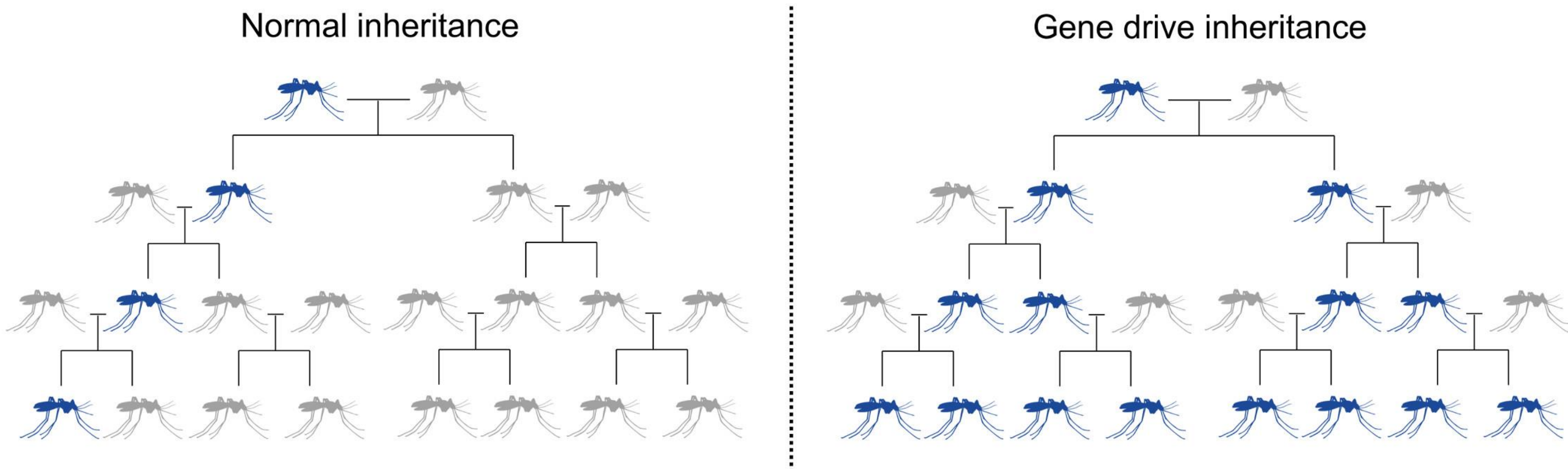
We support organisations
realizing the potential of biologicals
by implementing biorisk management
and complying with legal obligations
in an efficient and affordable way

Gene drive



- Study commissioned by the Netherlands Commission on Genetic Modification (COGEM)
- To map experience with gene drive systems, both natural and synthetic
- To inform the risk assessment

Different gene drive mechanisms have different features

Wolbachia	• restricted to merely arthropods • high drive efficiency (no true gene drive) • natural, cannot be engineered
Transposable elements	• low drive efficiency, high fitness cost
Underdominance	• high introduction frequency, high fitness cost • locally confined, removable
Meiotic drive	• moderate drive efficiency
MEDEA	• moderate drive efficiency • natural, synthetic versions are explored
Homing-based drives	• high drive efficiency, low release threshold • susceptible to resistance development • synthetic (by design!)

Results

Intended use:

- Population suppression
- Population replacement

Two separate factors:

- Gene drive: mechanism to spread beyond Mendelian laws
- Effector: element that induces an effect on the host organism; may be:
    - Gene drive itself (*e.g.* CRISPR/Cas inserting in an essential gene)
    - Payload gene (*e.g.* gene interfering with embryo development)

Considerations:

Effects on the gene drive host organism

- Off-target modifications (*e.g.* CRISPR/Cas inserting in non-target sequence)
- Interaction with host genome (*e.g. Wolbachia* in previously uninfected *Aedes aegypti*)
- Modified susceptibility (*e.g.* vectoring another disease)
- Stability of the gene drive system (*e.g.* unlinking driver from payload gene)
- Horizontal gene transfer (*e.g. Wolbachia* genome fragments to their insect host)

Considerations:

Effects on biodiversity

- (Non)-target organisms (*e.g.* elimination of the gene drive host organism with effect on *e.g.* predators, competitors, …; niche replacement; transfer to related species, …)

Resistance development

- To the gene drive system (*e.g.* variation/mutation of cleavage site of the CRISPR/Cas system)
- To the effector

Effects beyond the target area

- Dispersal (potential for low threshold drives)
- Options to limit dispersal (*e.g.* high threshold drive, reversal drive, ‘daisy chain’ CRISPR/Cas gene drive, …)

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Conclusions

- **Natural and synthetic** gene drives have been explored
- Field (cage) experiments and releases are almost exclusively with **mosquitoes**
- The most advanced programme is the release of *Wolbachia*-infected *Aedes aegypti* in several parts of the world to fight mosquito-vectored human diseases
- RA case-by-case as **different systems** have different characteristics

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Conclusions

- **Two elements**: gene drive as such and “load” or gene of interest

- Success of the system depends on:
  - the biology and population dynamics of the host organism,
  - the drive’s efficacy,
  - the fitness cost of the gene drive to the host,
  - the fitness cost of the load to the host,
  - environmental circumstances,
  - the potential for resistance development/presence in the target population.

These elements determine the speed and **limits of dispersal**

Conclusions

- **Mitigating measures** are being proposed/developed to limit and/or reverse the impact
- **No harmful effects** to human health or the environment have been observed so far
- Gene drives are **delicate constructs** and safeguards can be designed e.g. when working with CRISPR/Cas systems to avoid that they are created by chance
- **Concerns that the release of organisms with gene drives will inevitably lead to the suppression or replacement of all wild-type individuals should be nuanced**

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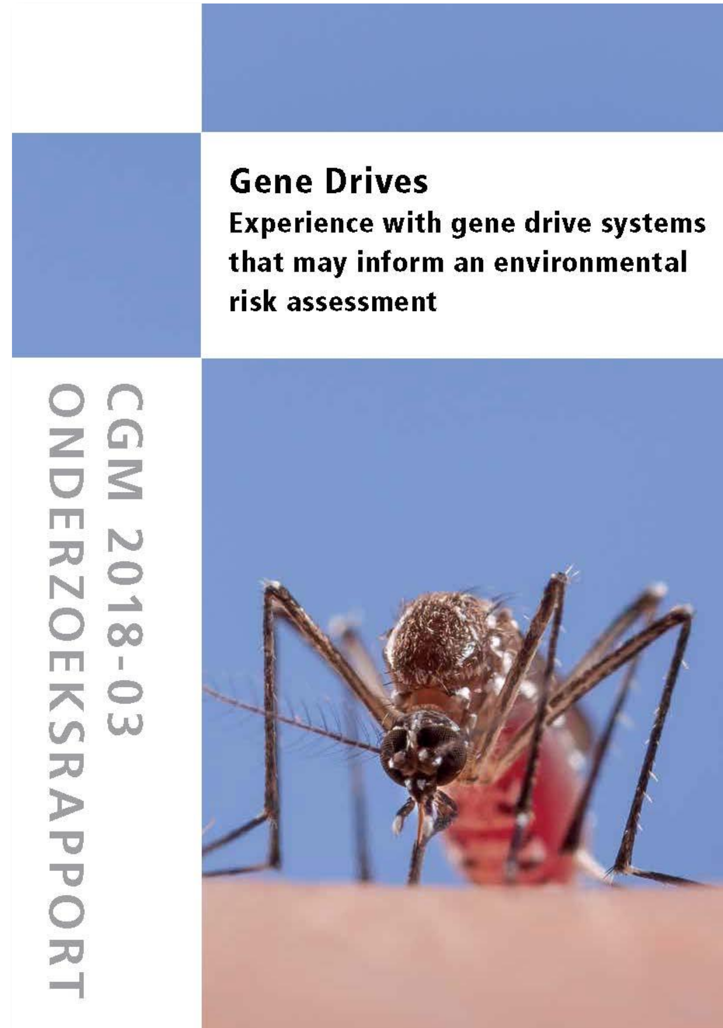

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