National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Risk Assessment and Management of Gene Drive Technology

Consequences for Contained Use

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Ministry of Health, Welfare and Sport

RIVM

Gene technology and Biosafety
GMO office

Tasks:

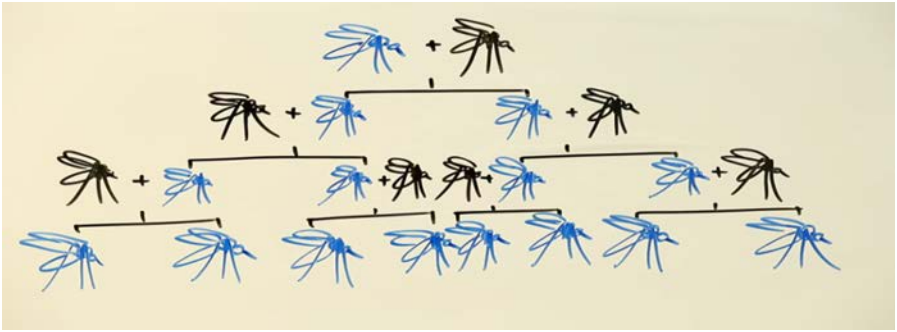
- Risk assessment of GMOs
- Policy advice to the Ministry on Modern Biotechnology

Gene Drive Technology

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.

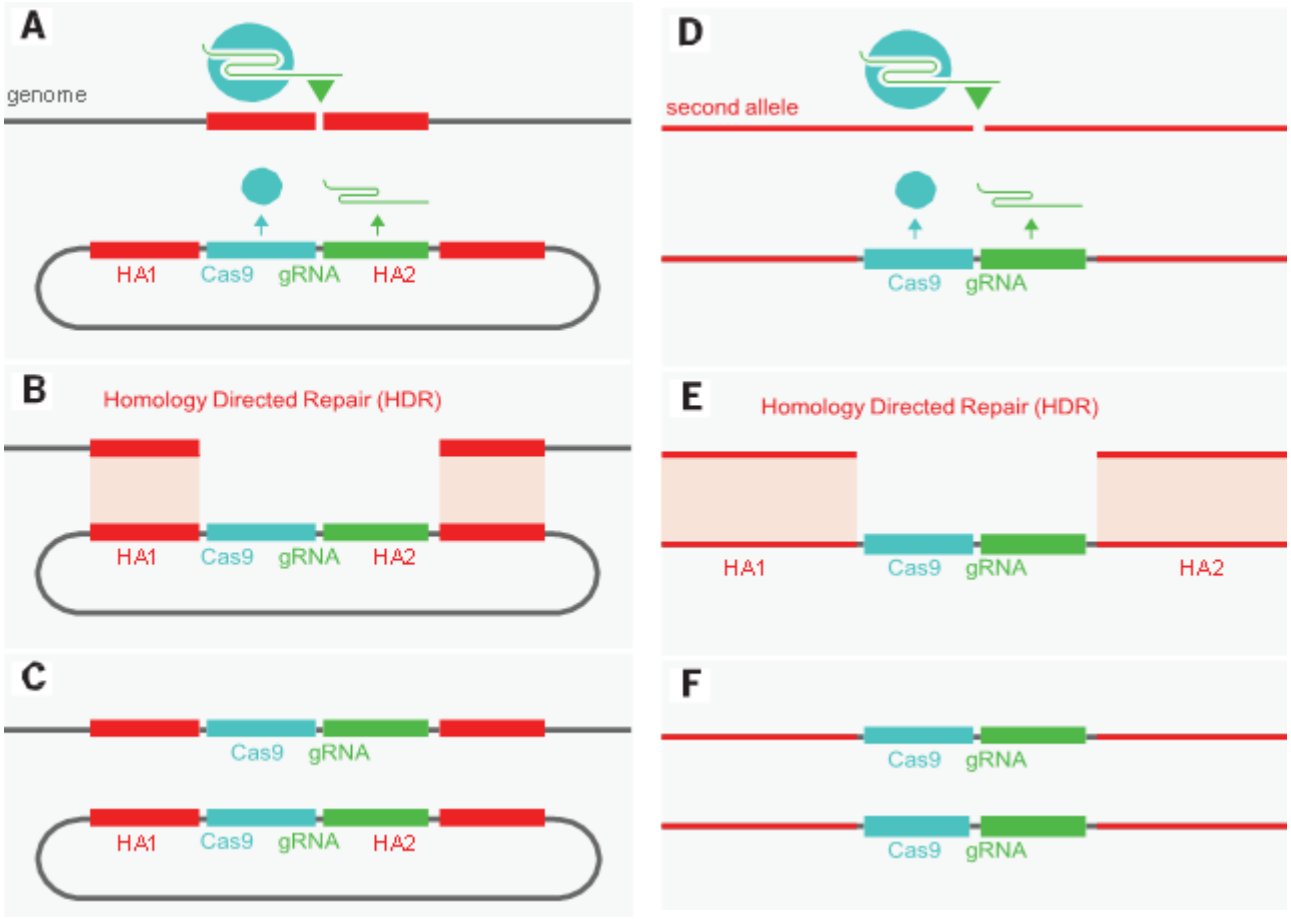
Examples:

- Homing endonuclease genes
- Transposons
- X-shredder, Medea



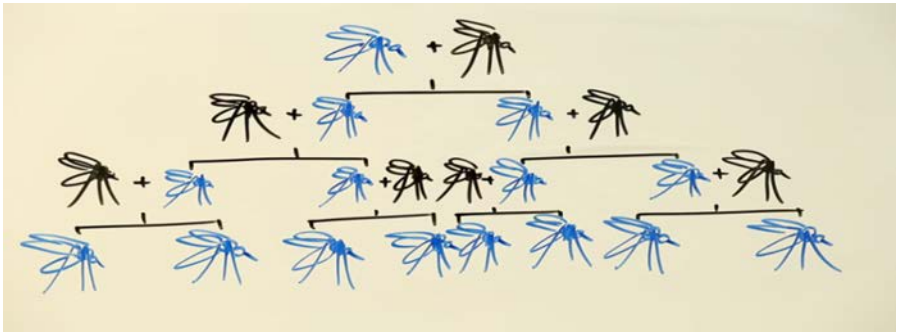
- CRISPR/Cas9 a new way to make an artificial gene drive

Mechanism of a CRISPR/Cas9 enabled gene drive



Gene Drive Technology

Powerful technique to potentially modify an entire population



Prerequisites:

- sexual reproducing organism
- HDR – cell repair mechanism
- short generation time
- population structure that facilitates the spread of the gene drive

Many proposals for a wide variety of challenging issues

Public Health

Conservation

Agriculture

Basic Research

Many proposals for a wide variety of challenging issues

Public Health

Conservation

Agri

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International activities

The National Academies of
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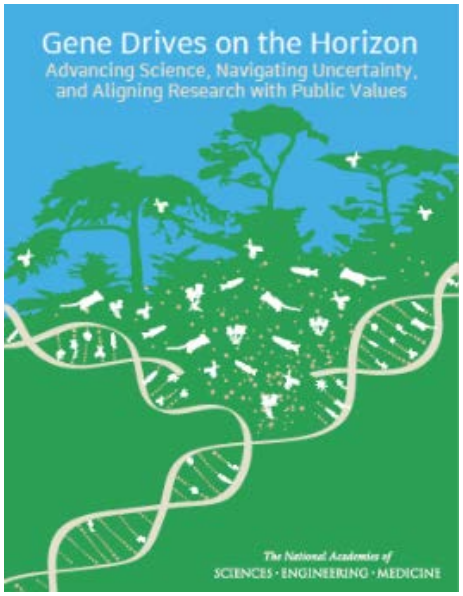


Australian Government
Department of Health
Office of the Gene Technology Regulator

CSIRO

Australian Government
Australian Pesticides and Veterinary Medicines Authority

CSIRO-RSN Symposium on the Use of Gene Drive Technology in Controlling Pests and Diseases

June 29th 2016, Discovery Centre, Black Mountain, Canberra

Policy Report, RIVM (Jan 2016)

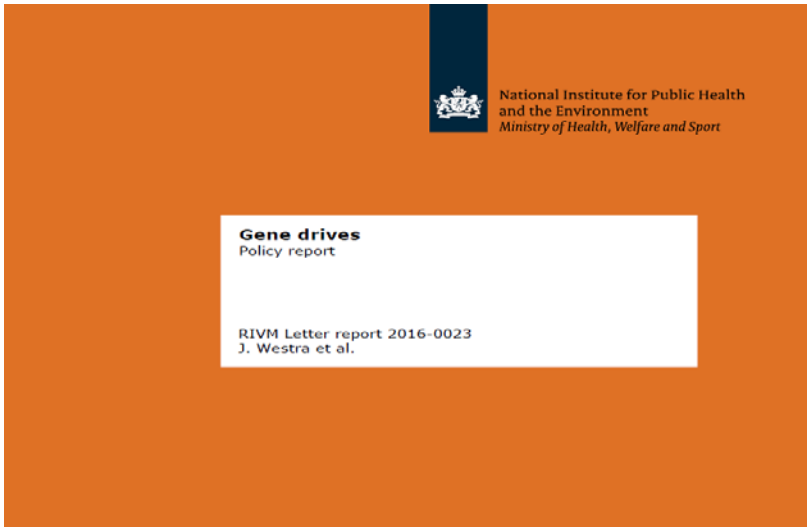
Position statement of the ZKBS, Germany (Feb 2016)

E-bulletin by HSE, UK (March 2016)

Lorentz meeting, Leiden NL (March 2017)

Many scientific publications

RIVM activities



Policy report (jan 2016)

Expert workshop on gene drive technology - contained use (jan 2017)

International context

RIVM

EU legislation provides sufficient opportunities to implement an effective risk assessment method

Potential consequences for human health and the environment can spread beyond national borders.

→ Debate on EU and international level

Ethical implications, Biosecurity

Environmental release

RIVM

Additional knowledge and information is needed to effectively assess potential environmental risks

- Other data to be generated, other expertise needed;
- Step-by step principle needs to be filled in in a different way.

Contained use

RIVM

Current assessment method for contained use activities is not (or partially) tailored to GMOs with a gene drive.

- Advise to the Ministry: Gene drive technology should require a permit (instead of a notification);
- Development of an adequate risk assessment method is needed.

Conclusions from the expert meeting:

International consistency on containment measures for gene drive organisms is important;

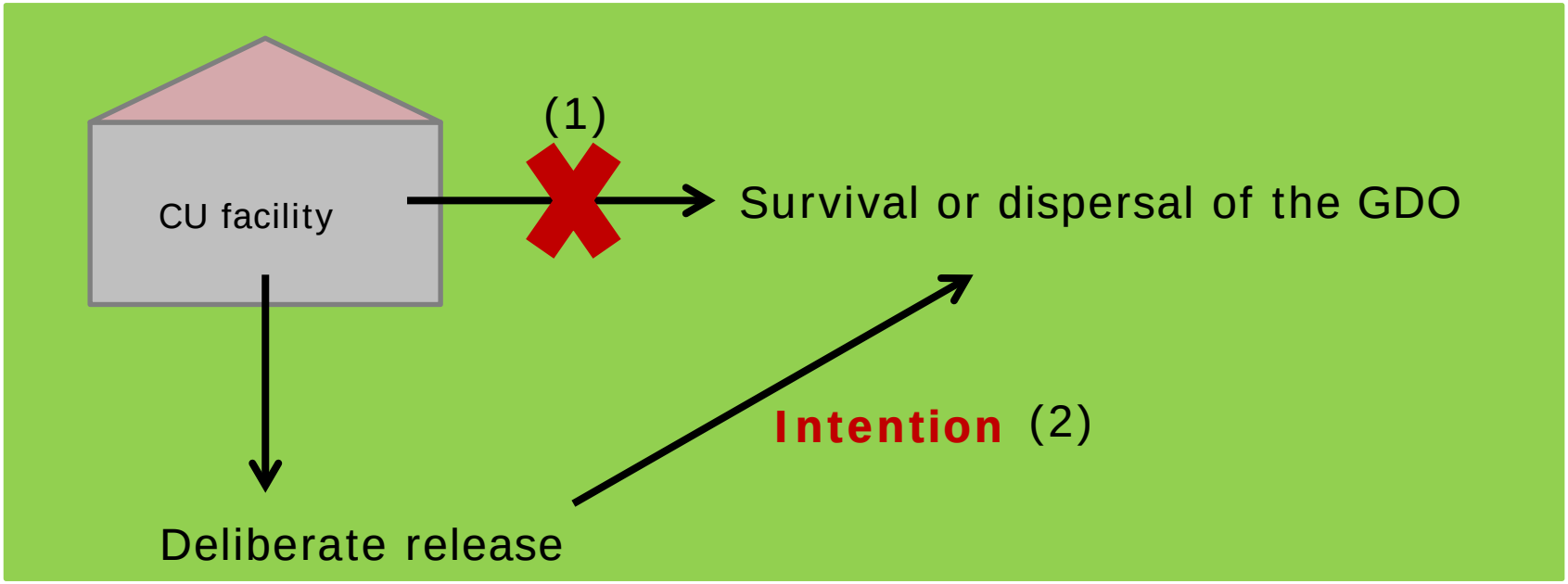
Streamlining risk assessment methods and procedures is useful.

Action by the Dutch Ministry

The national regulation for contained use is adapted (april 2016):

- Activities with ‘gene drive organisms’ (GDO) are defined as activities with any organism that is
  - capable of sexual reproduction,
  - is genetically modified with a DNA sequence that encodes a site-specific endonuclease, (in the case of the CRISPR/Cas9 gene drive technology a guide RNA (gRNA)
  - that integrates at a genome position within the cutting sequence of the endonuclease.
- This activity is a level 4 activity, thereby requiring a permit.
- Adequate control measures are determined by a case-specific risk assessment.

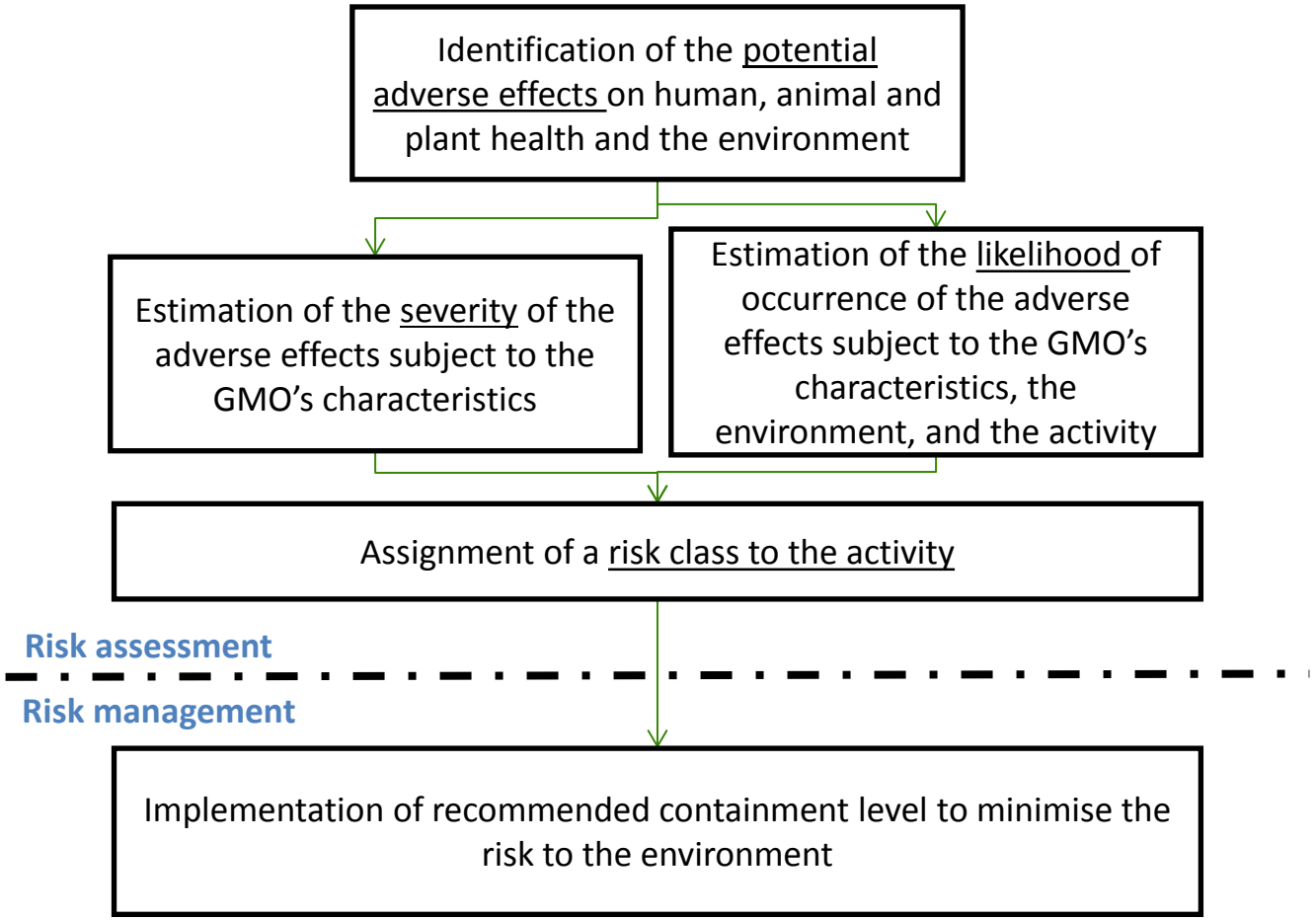
Contained Use (CU) versus Deliberate Release (DR)



(1): Risk Assessment (2009/41/EC)

(2): Environmental Risk Assessment (2001/18/EC)

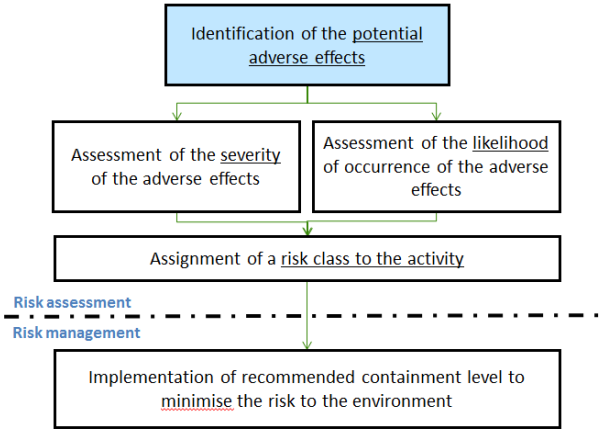
Risk assessment according to Dir. 2009/41/EC



Potential adverse effects of a GDO

Potential adverse effects which may occur upon an unintentional release:

1. Survival of the GDO in the environment
2. Genetic transfer of the gene drive elements to wild relatives

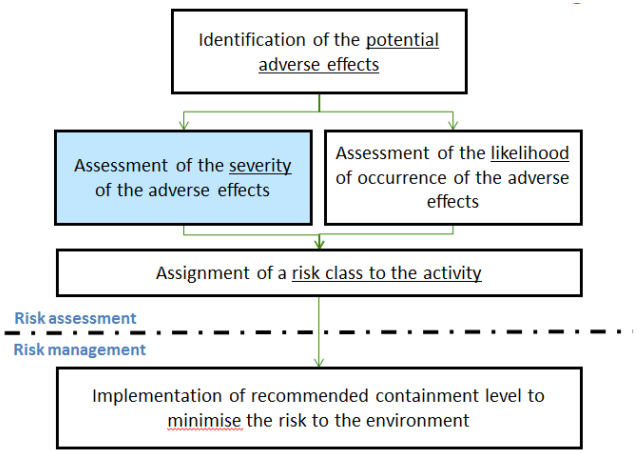


Severity of the potential adverse effects

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



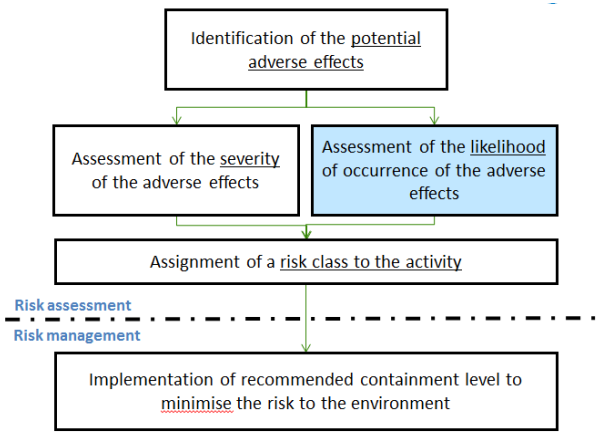
Severity is estimated from negligible – low – medium - high

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.

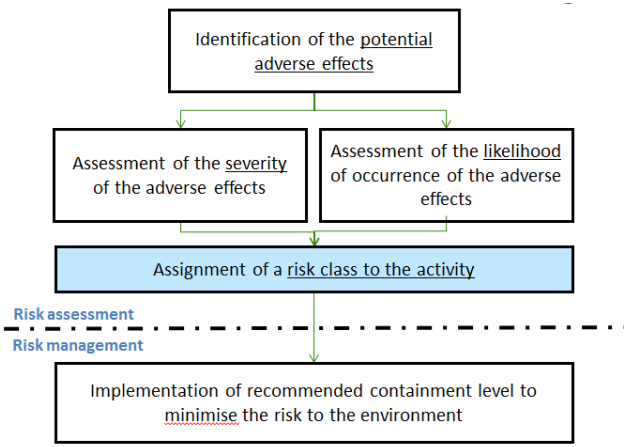
- the potentially exposed environment
  e.g. climate conditions, presence of mating partners, prevalence of the GD target site in the local population, etc.



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

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.

The risk level and class of contained use activities with a GDO					
		Severity of potential adverse effects (ecological impact)			
		Negligible	Low	Medium	High
Likelihood of occurrence of potential adverse effects	High	Negligible **Risk class 1**	Medium **Risk class 2**	High **Risk class 3**	High **Risk class 3**
	Medium	Negligible **Risk class 1**	Low **Risk class 1**	Medium **Risk class 2**	High **Risk class 3**
	Low	Negligible **Risk class 1**	Low **Risk class 1**	Low **Risk class 1**	Medium **Risk class 2**
	Negligible	Negligible **Risk class 1**	Negligible **Risk class 1**	Negligible **Risk class 1**	Negligible **Risk class 1**

Risk class 2: medium risk

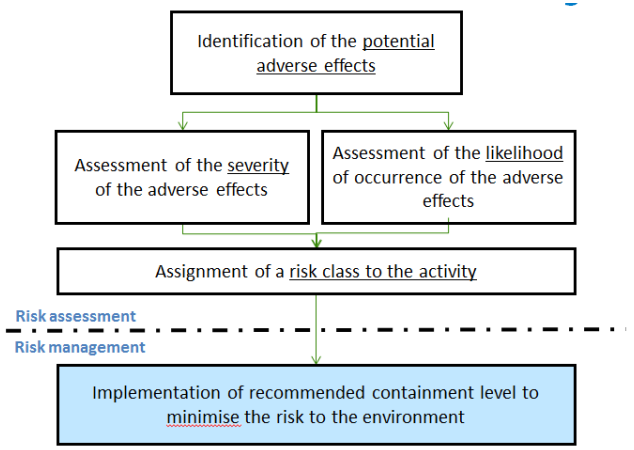
A non-permanent impact on the environment, i.e. the spread of the GDO or its trait is transient and the initial situation can be restored.

Risk class 3: high risk

A permanent and non-reversible impact on the envrionment

Risk management – Minimal control measures

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

(measures to prevent potential adverse effects due to pathogenicity can be omitted)

Risk management – Minimal control measures

	Minimal control measures		
	Risk class 1	**Risk class 2**	**Risk class 3**
Physical requirements	Two layers of physical containment: (1) species appropriate container (unbreakable, escape-proof) and (2) laboratory to include species-specific barriers	Additional layer of physical containment to enclose the species appropriate container	
			Two door system with interlock
Work practice		Access to all areas used for GDO activities limited to trained personnel and instructed service personnel	Access to all areas used for GDO activities restricted to trained personnel and accompanied service personnel
		Monitoring plan available to test for the presence of the gene drive element(s) in the environment in case of unintentional release	
			Emergency plan prepared in case of detection of gene drive element in the environment

Minimal measures in addition or as modification of the BSL and ACL containments are presented.

Species specific control measures

Additional specific control measures			
For work with yeast and filamentous fungi		All manipulations inside a class II biosafety cabinet	
			Airlock, laboratory at negative pressure relative to surroundings and HEPA-filtered exhaust
			The controlled area must be sealable to permit fumigation
For work with arthropods	Hanging curtain at laboratory-side of door	Two door system with interlock	
	Insects immobilized for handling		Insects immobilized for handling and handled inside closed containment (e.g. a tent)
		Program to monitor the effectiveness of escape prevention	
			Protocols are practiced with wildtype organisms before implementation
			All manipulations with GDOs to be observed by second trained individual to provide assistance and verify adherence to procedures
For work with rodents		Identification of animals (earmark, chip, etc) is recommended	Means to identify animals (earmark, chip, etc)
			Camera or window to monitor housing of rodents

The control measures are indicative

Risk assessment and management is case-specific

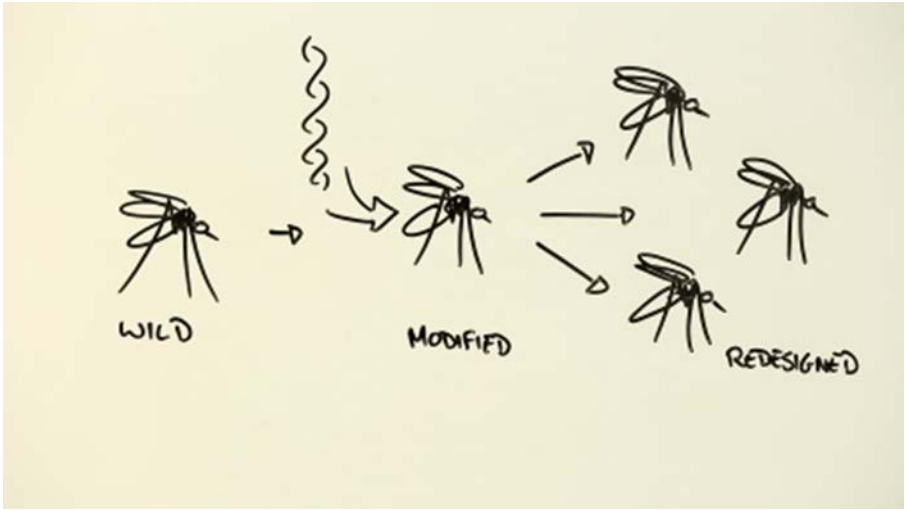
Conclusions

- Proposal for a structured risk assessment method for GDOs in contained use;
- The outcome presents new risk classes of GDOs and respective control measures (risk management).
- By working with several EU risk assessors together in developing this method a first step in a consistent approach is set.

- This work is submitted to *Applied Biosafety,*
- RIVM report in preperation with advice to the Ministry on specifications for risk assessment and management of GDOs.

- EU working group of the Regulatory Committee for Directive 2009/41/EC will be held at 14 December 2017; gene drive technology is on the agenda.

Thank you for your attention!



Proposed risk classes for a GDO

The risk level and class of contained use activities with a GDO					
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		Negligible	Low	Medium	High
Likelihood of occurrence of potential adverse effects	High	Negligible **Risk class 1**	Medium **Risk class 2**	High **Risk class 3**	High **Risk class 3**
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	Low	Negligible **Risk class 1**	Low **Risk class 1**	Low **Risk class 1**	Medium **Risk class 2**
	Negligible	Negligible **Risk class 1**	Negligible **Risk class 1**	Negligible **Risk class 1**	Negligible **Risk class 1**

Risk class 1: negligible to low risk

negl/low likelihood due to the characteristics of the activity, **or** GDO is unable to survive in local environment **or** GDO is unable to transfer the gene drive cassette to relatives.

Risk class 2: medium risk

medium likelihood due to the characteristics of the activity **and** medium impact of the GDO to the environment, **or**

by a combination of low likelihood with high impact (or v.v.)

Risk class 3: high risk

medium to high likelihood that adverse affect occurs due to an unintentional release **and** high impact of the GDO to the env. **or** combi of high likelihood with medium impact