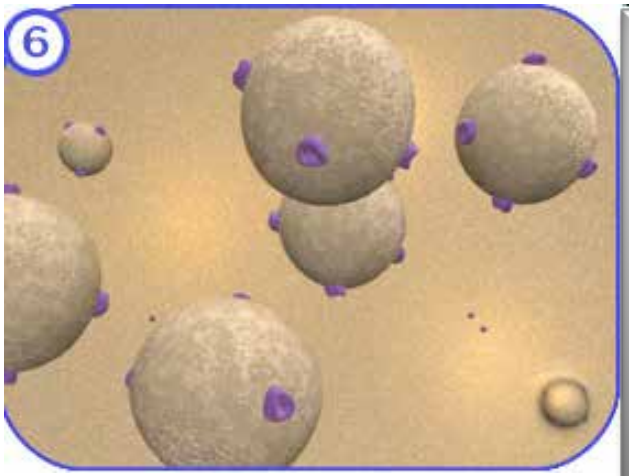
European Commission

Scientific Opinions on SynBIO in the EU

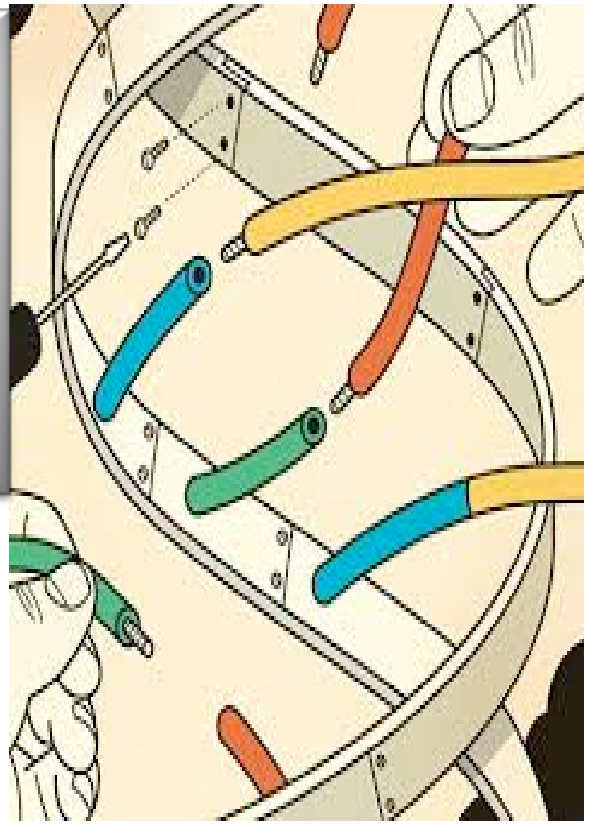
Conference on Planned Adaptive Regulation, London, 7-8 January 2016

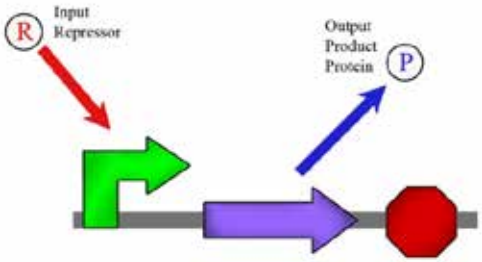


Theo Vermeire

National Institute for Public Health and the Environment

Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)





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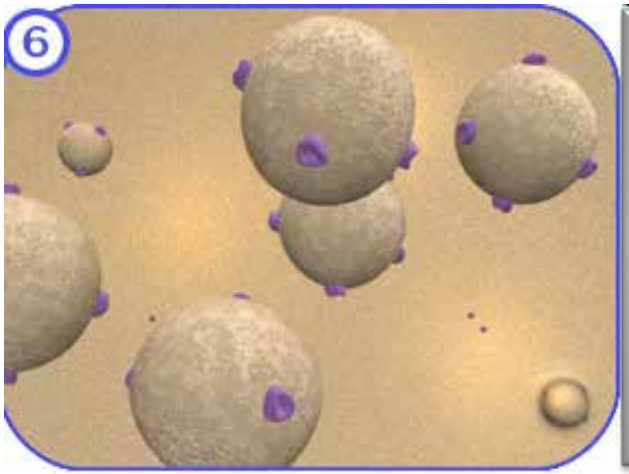
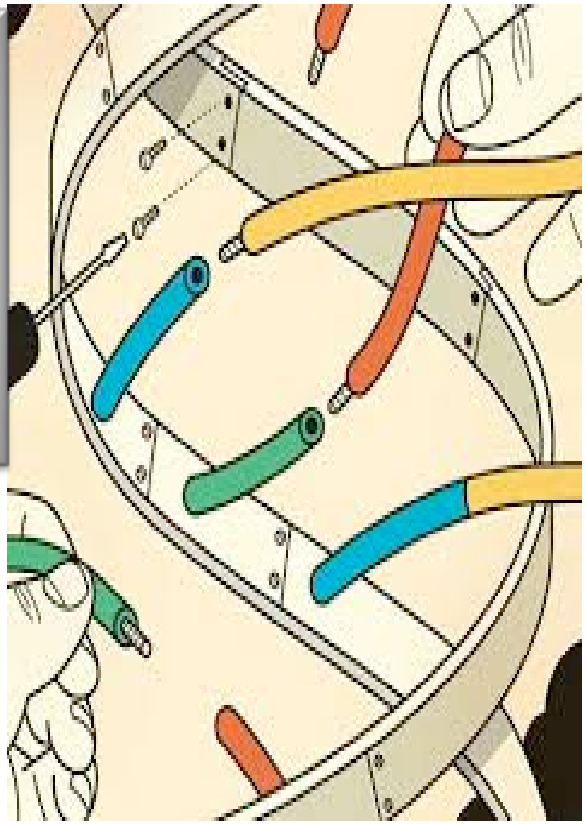
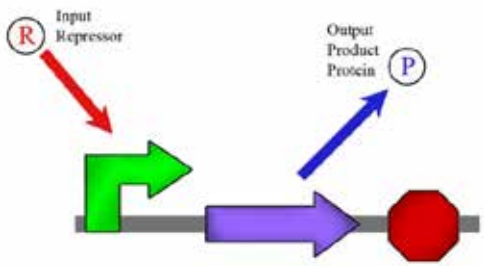


- Non-food SCs
- Mandate to SynBio WG
- Opinions

- Risk governance options

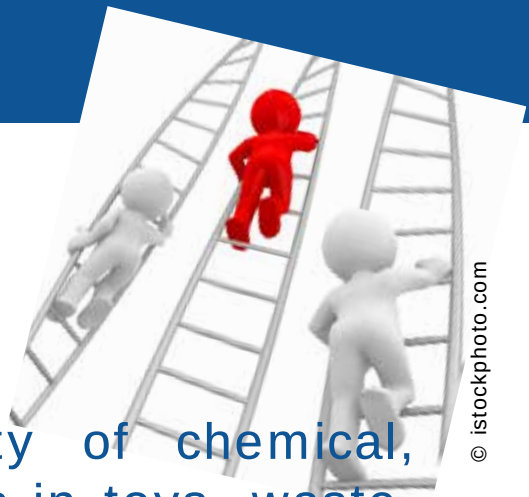




The European Commission non-food Scientific Committees (DG SANTÉ)

Health and Consumers

European Commission



Mandates of SCs

- **SCHER:** advice on toxicity and eco-toxicity of chemical, biochemical and biological products, chemicals in toys, waste, environmental contaminants, drinking water quality, indoor and ambient air quality, endocrine disrupters

- **SCENIHR:** advice on emerging risks, newly identified risks, complex or multidisciplinary issues requiring comprehensive assessment, issues not covered by other bodies

- **SCCS:** advice on risks related to consumer products (non-food) mostly on cosmetics but also on toys, textiles, clothing, household products, non-chemical risks (mechanical, physical, biological), consumer services (for example, tattooing, tanning devices)

WG SynBio

European Commission

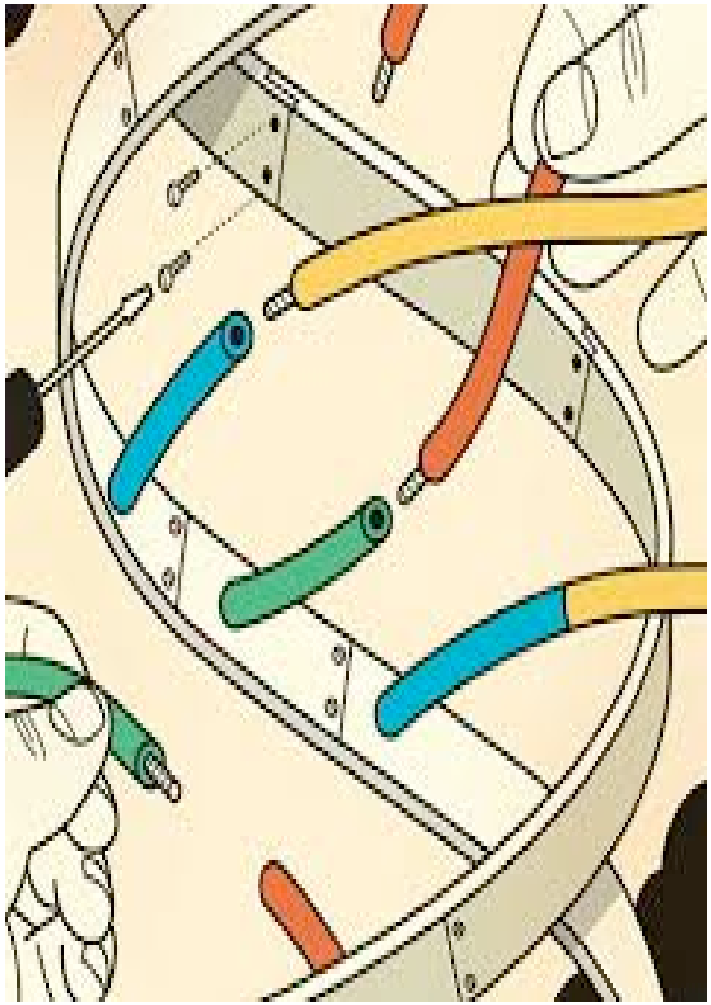
Mandate from DG SANTÉ, ENV, RTD, GROW

SCENIHR
Theo Vermeire (chair)
Michelle Epstein (rapporteur)
Philippe Hartemann
Ana Proykova
Eduardo Rodriguez Farre
Luis Martinez Martinez

SCHER
Colin Janssen
Teresa Fernandes

SCCS
Qasim Chaudhry
Maria Dusinska
Thomas Platzek
Suresh Chandra Rastogi
Jan van Benthem

External experts
Rainer Breitling
James Bridges
Camille Delebecque
Timothy Gardner
Katia Pauwels
James Philp
Markus Schmidt
Eriko Takano



Health and Consumers

The mandate I

Scope and definition of the phrase “SynBio”

1. What is SynBio and what is its relationship to the genetic modification of organisms?
2. Based on current knowledge about scientific, technical, and commercial developments, what are the essential requirements of a science-based, operational definition of “ SynBio”? These requirements should comprise specific inclusion and exclusion criteria, with special attention given to quantifiable and currently measurable ones.
3. Based on a survey of existing definitions, to wh ich extent would the definitions available meet the requirements identified by the Committee as fundamental and operational?

Adopted: September 2014

Health and Consumers

The mandate II è è Opinion II

European Commission

Methodological and safety aspects

4. What are the implications for human and non-human animal health and the environment of likely developments in SynBio resulting or not in a genetically modified organism as defined in the Directive 2001/18/EC?
5. Are existing methodologies appropriate for assessing the potential risks associated with different kinds of activities, tools, products and applications arising from SynBio research?
6. If existing methodologies are not appropriate to assess the potential risks associated with activities related to and products arising from SynBio research, how should existing methodologies be adapted and/or completed?
7. How, when, and to what extent can safety (safety locks) be inherently built into products of SynBio?
8. The SCENIHR, SCHER, SCCS are asked to draw the blue print of a general procedure/strategy for designing inherently safe applications of SynBio

Adopted: April 2015

Health and Consumers

The mandate III è Opinion III

Risks to the environment and and research priorities

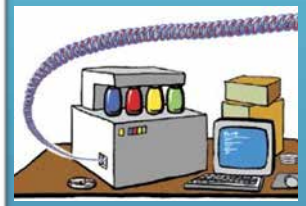
9. The SCENIHR, SCHER, SCCS are asked to review the state of the scientific knowledge concerning specific risks to the environment and synthesise it following the procedure and the requirements mentioned in the Decision XI/11 of the Convention of Biodiversity and include the synthesis in its opinion.
10. What are the major gaps in knowledge which are necessary for performing a reliable risk assessment in the areas of concern?
11. SCENIHR, SCHER, and SCCS are requested to provide research recommendations o n the main scientific gaps identified The recommendations should also include methodological guidance on the experimental design and on the requirements of the proposals, in order to ensure data quality and comparability, as well as the usability of the results for risk assessment.

Adopted: December 2015

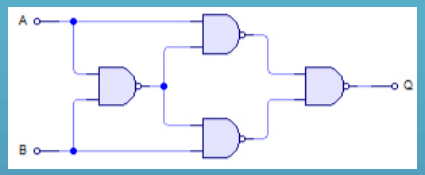
SCOPE

European Commission

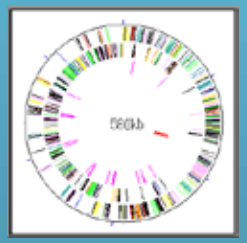
- Safety
- Foreseeable future
- Developments:



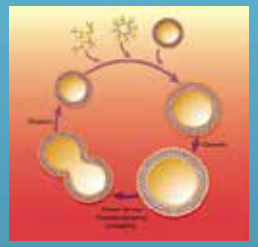
DNA-synthesis



Genetic parts / editing



Minimal cells



Protocells

Xenobiology

DIY

No questions on:

- **security,**
- **social, governance, ethical implications**
- **human embryonic research**

Opinion I

European Commission

SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms.

- No focus on conceptual ideas like modularisation or standardisation
- For the risk assessment, an operational definition of SynBio is provided, which is derived from the working understanding of SynBio as a collection of conceptual and technological advances that aims to enable **faster and easier design and manufacturing** of GMOs. SynBio is seen as an **extension of GM**.
- It acknowledges the **large existing body of regulations, RA and safety guidelines** for biological and genetically modified material
- It also acknowledges that these guidelines need periodic updates due to the rapidly advancing nature of GM technologies.
- It therefore supports the need for on-going updates of risk assessment methods.

When talking to regulators and the public, synthetic biologists tend to emphasize “continuity with the past” and safety; when talking to prospective funders, they emphasize novelty (Tait 2009, 150).

Even within scientific communities, there are differences of opinion whether synthetic biology is revolutionary or an incremental advancement of biotechnology (Zhang et al. 2011).

OPINION II

European Commission

Question 4: What are the implications for human and animal health and the environment of likely developments in SynBio resulting or not in a genetically modified organism as defined in the Directive 2001/18/EC?

New challenges in predicting risks are expected due to emergent properties: e.g.,

- **the integration of protocells into/with living organisms,**
- **future developments of autonomous protocells**
- **the use of non-standard biochemical systems in living cells**
- **the increased speed of modifications by the new technologies for DNA synthesis and genome editing**
- **the rapidly evolving DIYbio citizen science community à increased probability of unintentional harm.**

OPINION II

European Commission

Question 5: Are existing methodologies appropriate for assessing the potential risks associated with different kinds of activities, tools, products and applications arising from SynBio research?

The existing risk assessment methodologies, in particular for GMOs and chemicals, are applicable

However, several SynBio developments will require improving existing methodology: such as

- **combining genetic parts and the emergence of new properties due to interactions (genetic parts libraries),**
- **combinations of chemical and biological assessments (protocells),**
- **interactions between xenobiological and natural organisms (xenobiology),**
- **and the acceleration of GM processes**

OPINION II

Question 6: If existing methodologies are not appropriate to assess the potential risks associated with activities related to and products arising from SynBio research, how should existing methodologies be adapted and/or completed?

The SCs suggest several improvements to ensure continued safety protection proportionate to risk, while enabling scientific and technological advances in the field of SynBio.

1) support the characterisation of the function of biological parts and the development of computational tools to predict emergent properties of SynBio organisms,
2) streamline and standardise the methods for submitting genetic modification data and genetic parts information to risk assessors,
3) encourage the use of GMOs with a proven safety record as acceptable comparators for risk assessment,
4) aim to ensure that risk assessment methods advance in parallel with SynBio advances, and
5) support the sharing of relevant information about specific parts, devices and systems with risk assessors

OPINION II

European Commission

Question 7: How, when, and to what extent can safety (safety locks) be inherently built into products of SynBio?

Currently available safety locks used in genetic engineering such as genetic safeguards (e.g. auxotrophy and kill switches) are not yet sufficiently reliable for SynBio.

- Notably, SynBio approaches that provide additional safety levels, such as genetic firewalls may improve containment compared with classical genetic engineering.

- However, no single technology solves all biosafety risks and many new approaches (e.g. additional layers of biocontainment) will be necessary. A careful evaluation of all possible dimensions (educational, behavioral, technological, economic, etc.) is warranted on a case-by-case basis.

OPINION II

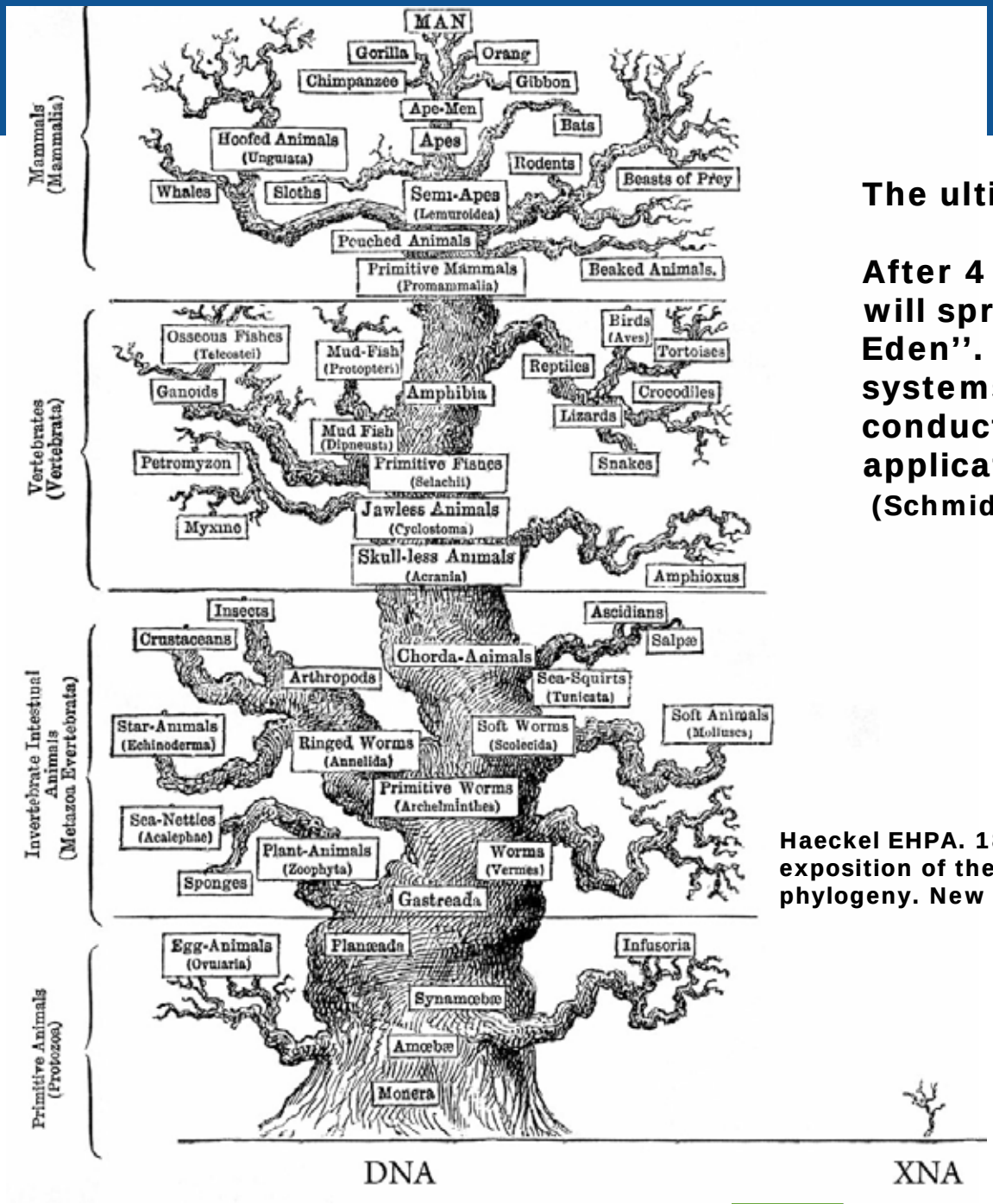
European Commission

Question 8: The SCENIHR, SCHER, SCCS are asked to draw the blue print of a general procedure/strategy for designing inherently safe applications of SynBio.

A blue print of a general strategy for designing inherently safe applications of SynBio is demanding, because of the stochastic and probabilistic character of the underlying biochemical SynBio processes.

General biocontainment approaches are based on:
1) physical containment,
2) inhibition of uptake,
3) incorrect translation,
4) inability to replicate,
5) absence of host immunity
6) endogenous toxicity.

Genetic safeguards such as auxotrophy and kill switches are not sufficiently reliable/robust for field release of engineered bacteria, because of mutation and positive selection pressure for mutants that may lead them to escape safeguards. The SCs recommend a clear strategy for the analysis, development, testing and prototyping of applications based on new forms of biocontainment and additional layers of containment using orthogonal systems.



The ultimate biosafety tool?

After 4 billion years, a new tree will sprout in the ‘‘Garden of Eden’’. Non-DNA-based biological systems will be a safer place to conduct SB experiments and applications
(Schmidt, 2010)

Haeckel EHPA. 1883. The evolution of man; a popular exposition of the principal points of human ontogeny and phylogeny. New York: D. Appleton and Company.

OPINION III

Question 9: To review the state of the scientific knowledge concerning specific risks to the environment and synthesize it following the procedure and the requirements mentioned in the Decision XI/11 of the Convention of Biodiversity and include the synthesis in its opinion

1. *Potentially negative impacts on objectives of Convention on Biological Biodiversity and Aichi Biodiversity targets (largely coincides with UNEP/CBD/COP/12/INF/11 and CBD Technical Series No. 82):*
   - Bioenergy, agricultural and chemical industry applications à significant land-use changes towards feedstock production
   - Accidental releases
   - Destablised conservation efforts and diminished support for conservation through SynBio varieties of organisms, including de-extincted species, and products

2. *Potential risks to the environment:*
   - Accidental release à persistence of SynBio organisms designed for environmental release, such organisms becoming invasive or disruptive for food webs
   - Transfer of genetic material via vertical gene flow or horizontal gene transfer
   - Emergence of new and uncharacterised biological functions, properties and products and absence of appropriate comparator organisms
   - Increased probability of unintentional harm by citizen science
   - Organisms cannot be retrieved once released and escaped to the environment
   - Firewalls, being genetic or using other techniques, cannot solve all biosafety risks. New forms of biocontainment required

OPINION III

European Commission

Question 10. What are the major gaps in knowledge to be filled for performing a reliable risk assessment in the areas of concern?

- Lack of information and tools for predicting emergent properties of complex non-standard systems
- Lack of information and tools for measuring the structural differences between the original (natural) and the engineered organism
- Full mechanistic understanding of underlying principles of semantic containment, and therefore the strength of semantic containment, is missing
- Challenges for risk assessment from use of genome editing methods in a multiplexed fashion (large number of variants, genome-wide modification, more pervasive changes to genomes)
- Degree of risk reduction through use of genetic firewalls
- Method for submitting genetic modification data and genetic parts information are largely natural language. Such practices could limit the sophistication of quantitative analyses, data evaluation, efficiency and effectiveness of risk assessment
- Citizen science: compliance with established biosafety rules

OPINION III

Question 11. SCENIHR, SCHER, and SCCS are requested to provide research recommendations on the main scientific gaps identified. The recommendations should also include methodological guidance on the experimental design and on the requirements of the proposals, in order to ensure data quality and comparability, as well as the usability of the results for risk assessment.

http://ec.europa.eu/health/scientific_committees/index_en.htm

Personal views

Idea

Development

Buy this!

Fortune and wealth

Oops

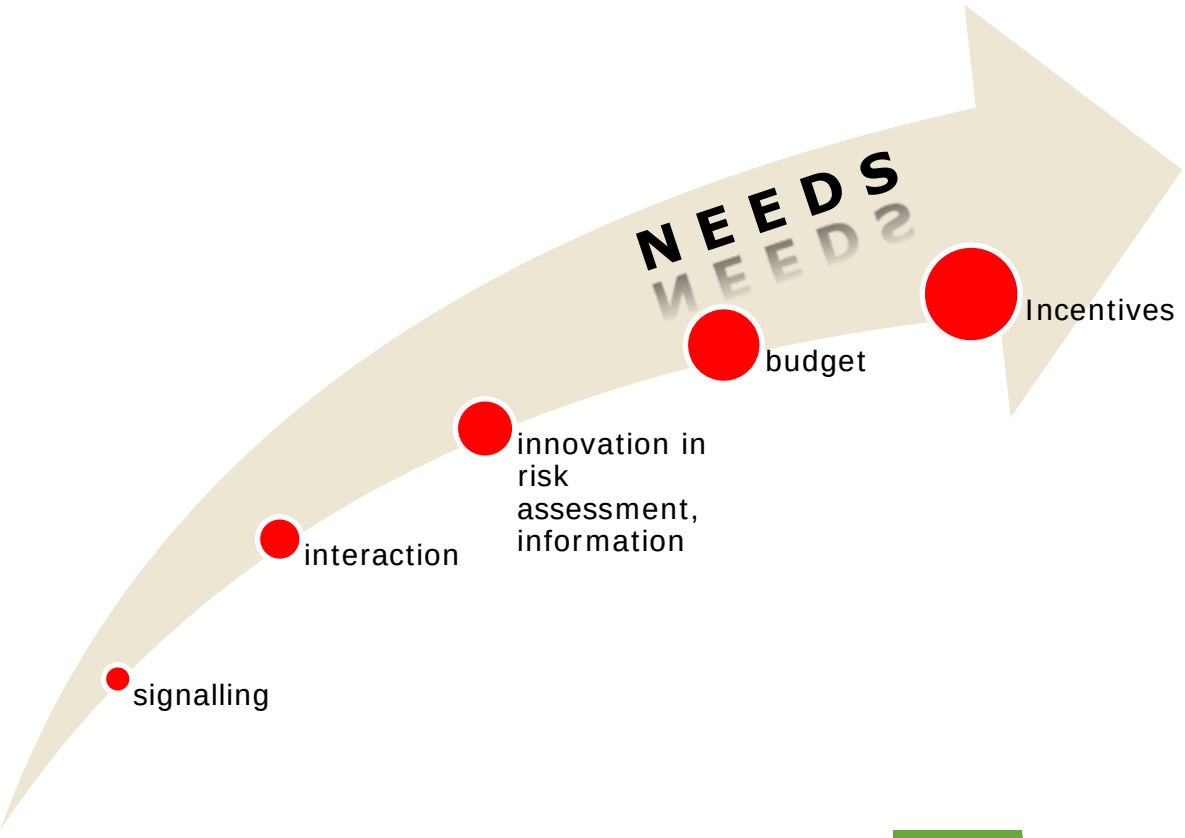
Public resistance

Uncertainty about risk

Politics

Regulation

Characteristics



- New risk
- Uncertain risk: lack of knowledge
- Value-ladenness
- Ethical issues
- Precautionary principle may apply
- Different frames
- Risk related research tiny fraction of R&D budget
- Regulation (partly) in place (GM)
- Highly innovative, fast progress
- Great promises
- Safety and innovation to be approached together
- Stakeholders with different interests

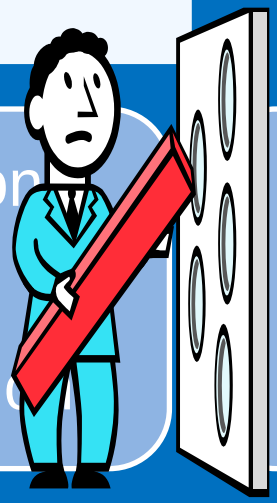
Is it safe?

Is it safe ?
or
It is (not) safe !

REGULATORY REQUIREMENTS as SIEVE

R&D

Regulation
&
Registrati



Market

Safe Innovations Governance model based on risk governance and stage-gate innovation model (under development at RIVM)

Idea → Gate 1 → Stage 1 Basic research → Gate 2 → Stage 2 Research feasibility → Gate 3 → Stage 3 Technology development → Gate 4 → Stage 4 System development → Gate 5 → Stage 5 Launch and operations

Safe Innovations Approach (SIA)

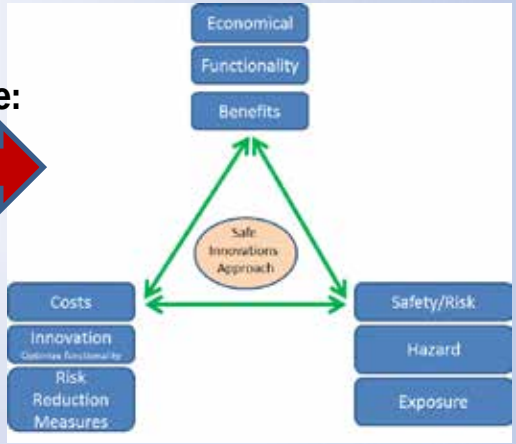
Safe by Design

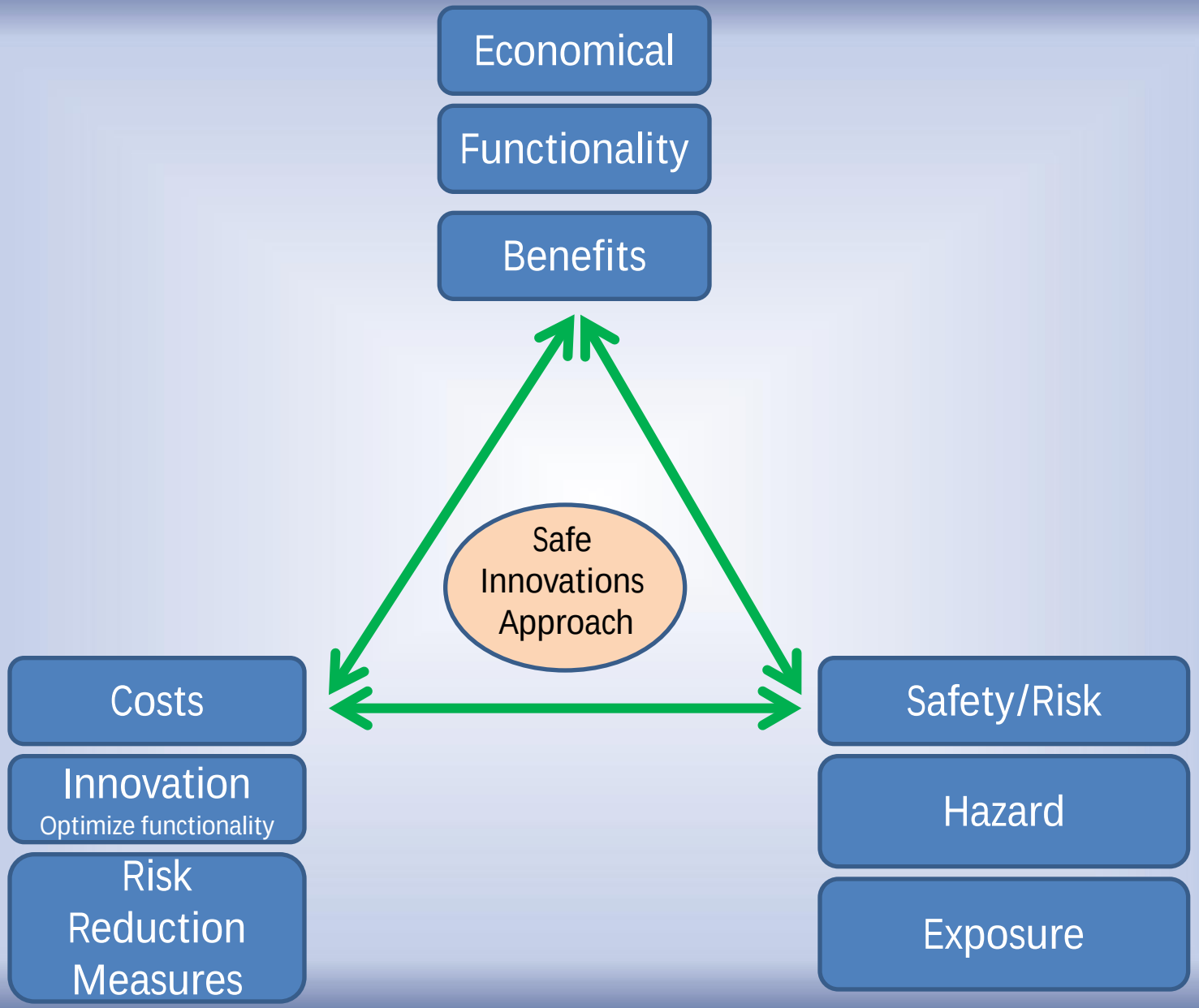
- Identify uncertainties
- Manage and downscale uncertainties and risks as early and as much as possible

Regulatory Preparedness

- Timely interaction between innovators and regulators
- Safe Houses

Per decision gate:




Economical
Functionality
Benefits
Safe Innovations Approach
Costs
Innovation
Optimize functionality
Risk Reduction Measures
Safety/Risk
Hazard
Exposure

T H A N K Y O U