



Adaptive Biosafety Assessment as a Learning Process

Strategy Paper

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SYN-ENERGENE

Synthetic Biology – Engaging in Responsible Governance of New and Emerging Science and Technology
in Responsible Governance of the Science and Society Relationship

Preface

Synthetic biology enables scientists to do experiments with biological systems that differ essentially from naturally occurring ones, which may no longer be the type of well-known and well-characterized organisms we have been dealing with so far. This calls for reconsideration of existing approaches in biosafety assessment. At the same time, several enabling tools such as gene editing techniques and bio informatics have resulted in a considerable increase in the speed of developing new technologies and applications, which makes it hard for risk assessors, risk managers and policy makers to keep pace. On top of that, the GMO debate has taught us that policies on controversial technologies require governance approaches that include safety as well as normative issues in the process of research and innovation.

To deal with this complex of issues in a dynamic societal and political setting in a responsible way, i.e. developing governance on safety and societal impacts along with developing new technologies and applications that may be beneficial for society, calls for assessment and management strategies that are adaptive.

The SYNENERGENE project aimed to contribute to the design of a learning process regarding such adaptive strategies that involves researchers, regulators, risk assessors, stakeholders as well as civil society with a workshop and interviews with experts in the field of synthetic biology and governance as well as stakeholders. This resulted in the "Adaptive Biosafety Assessment as a Learning Process - Strategy Paper".

Since this strategy paper is meant to take the process of designing and testing adaptive risk assessment and risk management strategies a few steps further, it is freely available for download at the SYNENERGENE website (www.synenergene.eu), together with a working document that was used for preparation of a workshop, a report of this workshop and a report of a number of interviews with experts and stakeholders.

- Adaptive Biosafety Assessment as a Learning Process - Strategy Paper
- Annex 1: Adaptive Risk Assessment in Synthetic Biology – Summary of interviews, January/February 2017
- Annex 2. Adaptive Risk Assessment in Synthetic Biology – Workshop Report, Amsterdam, June 23, 2016
- Annex 3. Adaptive Risk Assessment in Synthetic Biology – working document

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1. Introduction

The issue of biosafety of synthetic biology (synbio) has been discussed on different occasions during the past years. So far, the view of most experts is that existing approaches used in the risk assessment of genetic modification can be applied to experiments in synthetic biology too. At the same time, many experts recognize that the nature of innovative and emerging synbio technologies is uncertain (SCENIHR, 2014). Synthetic biology enables scientists to do experiments with biological systems that differ essentially from naturally occurring ones (Pauwels *et.al.*, 2013), which may no longer be the type of well-known and well-characterized organisms we have been dealing with so far. The Scientific Committees concluded that: *"...complexity and uncertainty are characteristic parts of the risk assessment of Synbio and have led the Scientific Committees to conclude that within the scope of current GMO regulations, risk assessment is challenging, e.g. because of the lack of 'comparators' and the increasing number of genetic modifications and engineered organisms."* (SCENIHR, 2014).

Several authors of essays and papers focusing on the social and ethical dimensions of synthetic biology have emphasized that this technology triggers similar issues and is / will be perceived as controversial as genetic engineering. The GMO debate has taught us that policies on controversial technologies require governance approaches that include safety as well as normative issues.

This calls for a pro-active attitude in which we anticipate future developments and a transparent, iterative process of risk governance, which includes risk assessment and dialogue among stakeholders including civil society globally (König *et.al.*, 2013, SANCO, 2012). These are key elements of Responsible Research and Innovation practices which is also a learning process. The challenge is to find ways in which the development of knowledge, expertise and strategies needed for risk assessment keeps pace with developments in synthetic biology research.

In order to develop risk assessment approaches along with new developments in synthetic biology, SYNENERGENE aimed to contribute to the design of a learning process that involves researchers, regulators, risk assessors, stakeholders as well as civil society with a workshop and interviews with experts in the field of synbio and governance as well as stakeholders.

This strategy paper presents the result of a few steps in an ongoing learning process. As such it is also meant to take the process of designing and testing adaptive risk assessment and risk management strategies a few steps further.

The second chapter of this paper briefly describes the activities this paper is based on. The chapters 3 – 6 summarise arguments and suggestion gathered from the workshop and interviews. Chapter 3 puts the risk discussion in perspective and chapters 4 and 5 focus on technologies and applications requiring attention from the perspective of risk assessment, and

the methodological, technical and organisational needs. The final chapter 6 explores how risk assessment in synbio could be put in a governance context.

1. Methods

On June 23, 2016 in Amsterdam a combined expert-stakeholder workshop was held on Adaptive Biosafety Assessment for synthetic biology. This date was chosen because it was prior to the SYNENERGENE Forum on June 24-25, 2016 in NEMO, Amsterdam, thus enabling international participation in the workshop.

This workshop was meant to address needs for future risk assessment as part of a mutual learning process on applying principles of Responsible Research and Innovation.

About ten experts in regulatory and governance issues in synbio was invited, as well as a number of participants from industry and the CSO community. Unfortunately, CSOs could not attend because of a specific CSO workshop organised by the ETC Group on the same day.

The workshop was attended by 2 participants from a Competent Authority and a scientific Advisory Committee, 4 independent scientists, 1 person from industry + 2 SYNERGY team members (chair and rapporteur) ([see Annex 2](#))

A working document outlining the goals and key topics to be discussed in the workshop and providing some background was sent to the participants 2 weeks before the workshop ([see Annex 3](#)). The results of the workshop are presented as a report that will be anonymised and may lead to further activities in this form.

In January and February 2017 eight experts and stakeholders were interviewed to complement the results with further comments and suggestions. These interviews were used to complement the findings from the workshop with a broader range of views and to add more depth to topics already discussed at the workshop ([see Annex 1](#)).

2. The risk discussion, definitions and the regulatory discussion

Currently many discussions are focusing on definitions of synthetic biology and the scope of existing regulations related to several specific emerging technologies such as CRISPR-Cas. It is true that in the context of risk assessment definitions and scope are relevant for legal reasons: Definitions and scope define when procedures that include risk assessment requirements apply to experiments and applications. But it is not easy to draw a hard line between 'conventional biotechnologies', including recombinant DNA technologies, and synthetic biology: it is more of a continuum. New methods and technologies allow for deeper intervention and the creation of living systems that are further away from natural systems.

The workshop participants and several interviewees agree with previous reports stating that current applications –for instance in enzyme production- and most of technologies and applications that is developing can be properly assessed with the tools provided by existing GMO regulation. This does not exclude the possibility that in the long run we may get to introducing new risks. Whether that is the case or not has to be decided on a case-by-case basis.

Therefore, the risk discussion must focus on specific technologies and applications, although it is hard to carve that of, especially when you are dealing with a process-based regulatory regime. In the words of one of the interviewees: “In discussing how to do a risk assessment it is not so much the definition that counts as well as the question: What is different about the application?”

Risk assessments still must be done case-by-case, gathering understanding of what these differences are and what their impact is, so over time we can decide what is still of concern and what is not, what to focus the assessment on and how to assess. This brings us to the need for adaptiveness.

3. Technologies and applications requiring attention

Before getting to the specific technologies and applications that require attention from a risk assessment perspective some general observations and concerns made by workshop participants deserve to be mentioned.

3.1. General observations and concerns

- **Protection goals:** There should be clarity about what we want to protect. Which biodiversity?
- **Increased complexity and the familiarity principle**, which is key in GMO risk assessment. The level of novelty and the volume is increasing. New technologies make it possible to make a high number of changes and engineer more complex pathways in organisms by multiple modifications based on modularisation (biobricks). We cannot simply say that the effect of multiple changes is the same as the sum of individual changes. The impacts of applying of genetic circuits and modification of complex pathways may be hard to predict. Semi-synthetic host organisms may be so far off from natural organisms with a GRAS¹ status that it is no longer possible to use the **comparator approach** in risk assessment.

¹ GRAS = Generally Recognized as Safe

- **Interaction with the ecosystem:** The old paradigm of biology that assumes causal relationships between genes and characteristics / behaviour of organisms is usually not valid while operating in complex systems such as the eco system and result in too simplistic models.
- **Longitudinal effects** -survival in evolutionary perspective- and epigenetic effects must be taken into account.
- **The level of understanding of horizontal gene transfer:** The baseline scientific work on frequency of lateral gene transfer has only been enabled by the recent revolution of sequencing. Moreover, our understanding of environmental implications is in its infancy. As a consequence, the danger we are trying to protect ourselves against is not well understood;
- **Containment:** Many experiments with and applications of synthetic biology will be contained. However, the question is to what extend organisms can be really contained. Human failure is an important risk factor and the actual level of containment relies not on the prescribed facilities only but also on awareness and behaviour of lab personnel working with engineered organisms. That makes 100% containment virtually impossible, so what if one single escape can be fatal? Or should we not worry about incidental escape because we can assume limited fitness of engineered organisms in general?
- **Low costs and easy access to the technology** is driving **rapid development and diffusion**. We may also start seeing **small-scale applications** in and around the house that are difficult to monitor and control, such as packaging with biosensors;
- **Technical safe by design approaches** aiming for biological containment and limited activity of a modified organisms may look promising but there is doubt about its effectiveness: They may not work in natural environments that are complex and difficult to fit in (simplistic) predictive models and/or effectiveness may only be temporary. They may work under specific conditions, but what if the conditions vary. Compare it with cars: designed for safety does not avoid traffic accidents.

3.2. Technologies and applications that require attention

- Risks related to **gene drives** is deemed the most significant in new biotechnologies. One of the NGOs puts gene drives in a context of a bigger move towards systems where intervention happens in the field, which also includes RNAi applications. NGOs demand a moratorium on gene drives because the potential hazard is too great and we do not sufficiently understand the way populations and ecosystems may react. Interviewees also wonder how to collect relevant data for risk assessment of applications that are designed to survive and proliferate by active gene transfer in the environment in a safe (and

contained) way? The step-by-step approach, based on gradual decrease of containment measures, may no longer apply if the final goal is the opposite of containment. Several interviewees also express concerns about the effectiveness of so-called The effectiveness of localization strategies (i.e. to keep the organism from spreading) is yet unknown. However, one can also argue that gene drives does not involve new technologies; it's just an enlargement of the application field of genetic engineering that requires proper fitness assessment for the first experiments (in containment) and controlled step-wise introduction.

- A specific example is **Xenobiology** (non-natural DNA structures (XNA) and unnatural amino acids), which also makes it difficult to compare with existing organisms in terms of pathogenicity, reproduction capacity, speed of dispersion and chemical characteristics. We know little about its impact on biodiversity.
- **Epigenetics and gene editing**. There may be risks involved in changing the regulation of gene expression and editing multiple genes. One interviewee specifically mentions RNAi technology, which is not altering the organism's DNA but may have an impact on the ecosystem nonetheless.
- For **biosensors based on genetic circuits** the range of risk assessment would depend on their level of containment. **Medical applications** in personal health care require assessment of safety for the patient only if the application is contained by the patient, but would require also a risk assessment of the patient's environment if the organism or DNA can migrate.

Some topics and areas were mentioned by individual interviewees only, such as:

- **Biohacking**, which is potentially problematic when regulation is lacking or when specific technologies are deregulated. Together with lower access to the technology the emergence of crowd funding platforms resulting in better citizens' access to funding has created favourable conditions for citizens science, also in biotechnology. In the US DIY labs provide opportunities both to lay people and professionals. For the latter, working in DIY labs is interesting because of rapid funding opportunities. Moreover, in the US there is only guidelines on risks to follow.
- **Molecular communication and signalling systems**, for instance between plants and ecosystems, linked to gene switches that set a specific biomolecular reaction in motion.
- **De-extinction**: When claiming the possibility for re-introduction of species that have extinguished we should ask ourselves why these species have extinguished, which usually has to do with loss of habitat. It may be better to focus on the cause by saving habitats.

- **Engineering photosynthesis:** Although current assessment methodologies would still apply, enhanced photosynthesis may raise a new type of risk related questions.

4. Needs

The precautionary principle to risk management states that if an action or policy has a suspected risk of causing harm to the public, or to the environment, in the absence of scientific consensus (that the action or policy is not harmful), the burden of proof that it is not harmful falls on those taking that action. Competent authorities can decide to put a halt to synbio experiments and applications based on the precautionary principle to synbio. If combined with specific requests for experiments and specific risk research, such a moratorium is conditional and temporary.

4.1. Methodological needs

- **Endpoints** have to be defined. What are the effects on environmental systems and effects on health that should be assessed? This must start early because we need a baseline before we start applying new technologies of potential concern;
- **Apply the case-by-case** approach: Complete understanding and prediction of everything may not always be necessary if we apply a case-by-case approach by looking at each case very much the way we already do:
 - The type of use: in containment or release to the environment;
 - The type of product: purified products or still containing living modified organisms;
 - Applying containment levels in compliance with the hazard of accidental escape and uncertainties regarding risks;
 - A coherent approach based on existing experience.

4.2. Containment strategies

There is a need to further develop containment features that include design, testing, certifying and standardisation. These should be put against classes of containment technologies, such as:

- Limiting fitness of organisms on release by, for instance, auxotrophy (the inability of an organism to synthesize a particular organic compound required for its growth) and kill switches. As single mutations in kill switches may reduce their effectiveness, we know this is not enough. To assess the impact of mutations you have to test on multiple generations to come up with reliable results. For this reason, testing should begin early.
- Recoding: knocking down genes to create an organism that is so far off that the chance of lateral gene transfer is limited.

- **Localisation**: strategies to keep a gene drive from spreading need to be developed and tested. Examples of localisation strategies are immunisation drives, reversal drives or daisy-chain drives: a series of drives with different requirements where you control one aspect of it. Withhold a nutrient and it cannot spread beyond one area.

4.3. Measuring, modelling and facilities

- For the assessment of multiple changes in organisms and non-familiar hosts we need **techniques for analysis at a system level** such as ~omics techniques.
- There is also a need for **innovation in measuring and monitoring impacts**.
- **Advanced modelling** with the help of computer tools to process large data sets can add to the predictive value of risk assessment;
- **Modularisation**: The principle of modularisation may also produce conceptual tools for risk assessment.
- **Field trial locations for safe experiments**: There is a clear need to gather more experience with the release of GMOs to the environment. Several interviewees emphasize the need to look for off-target and unexpected effects in a more systematic way than we've done so far. More specifically, there is a need to rethink how we must evaluate the impacts of completely new organisms where we cannot apply the comparator approach. There is a need to have facilities, especially field trial locations where you can do relevant experiments in a safe way. Such facilities are not yet available.

4.4. Risk research funding and integration

- **Multidisciplinarity and integration in innovation programs**: There is currently little funding for risk studies in comparison with the funding of developing and applying new technologies and methods. A clear funding strategy for risk research is needed.
- **Integration of risk research in European and international research and innovation programs** and inclusion of ecologists and experts in epidemiology in trans and multidisciplinary teams. The program of Synbiochem - Manchester Synthetic Biology Research Centre *for Fine and Speciality Chemicals* in Manchester² and current plans at Wageningen University for integrating synthetic biology research, risk assessment and Responsible Research and Innovation could be inspiring examples.

² <http://synbiochem.co.uk/>

5. Governance and RRI as a learning process

5.1. General considerations

- In the end, it is a political decision to allow experiments and applications that involve new biotechnologies, which is usually the result of a balance of agreement on science based risk assessment, what kind and level of uncertainties are considered acceptable, how benefits are valued, ethical considerations and public opinion.
- In a situation of potentially large social benefits and high levels of uncertainty regarding and ignorance about potential hazards we should treat the introduction of new technologies as social experiments in which benefits and risks are identified, valued and monitored.
- Putting risks in perspective: There is a need to make a balanced analysis of risks and benefits for society. Are we solving a problem with the technology and its applications?
- The speed of technological development: Technologies are developing much faster than during the decades before. The first paper on gene drives, for instance, was published in 2014. Since then, several gene drives developed and there is large amounts of work going on in insects and worms, and already now some ideas on mammals³ are developing. At the same time a moratorium on research that does not meet containment criteria was introduced. On the other hand, the urgency of applying this technology to improve health in cases where available medicine is not effective, for instance in areas that suffer from malaria, is high. Therefore, it cannot be assumed that people will always adhere to 'good practice'. And although an increasing number of scientists are aware of the need to act responsibly and raise issues that require governance or oversight, it is becoming increasingly difficult for regulators and risk assessors to keep pace.

5.2. Management of risk research

- **Capacity in risk assessment**: Both EFSA and national Advisory Committees and Competent Authorities must handle an increasing number of applications under GMO regulation. A solution must be found for keeping up with legal time frames for evaluation while maintaining / improving the quality of the assessments.
- **Monitoring the field**: EFSA's Guidance on Post Market Environmental Monitoring of GMOs is an important tool to learn more about behaviour and risks must be implemented properly and systematically.

³ Kevin Esvelt proposes to create mice that are immune to the Lyme-causing pathogen, or to a protein in the tick's saliva, or both, to break the cycle of transmission ([New York Times, June 7, 2016](#))

- **Risk research should be made more attractive:** Risk research is usually publicly funded and not very attractive for independent scientists because (high ranking) scientific journals show little or no interest in publishing negative results or in publishing any risk research results at all. "We need a journal of failed experiments", one of the interviewees said.
- **Funding of risk research:** There is a need for public funding for risk research that keeps pace with technological development but we also should think of putting the responsibility for risk research to those who develop and apply the technologies.
- **Room for curiosity driven research:** One of the interviewees warns that there is limits to applying RRI requirements to research. There is a need for fundamental and innovative curiosity driven research which, at a stage where applications and benefits are still unclear, risks being hampered by all kinds of socio-economic and ethical requirements.

5.3. Integrated approaches and learning process

- Because of the rapid diffusion of the technology **pre-regulatory discussion in a non-official setting must be facilitated.** That requires an organisation with reach to take care of international issues that tend to fall between the cracks and:
 - that is broad enough to cover all relevant issues and discuss cross-boundary effects,
 - that is sufficiently trusted and independent from industry,
 - where information and views can be exchanged in a relatively congenial setting,
 - that is flexible enough to assess emerging synbio technologies rapidly,
 - that is able to push safe design approaches.
- **Integrated approach of normative issues:** Governance strategies should integrate (adaptive) risk assessment and management strategies and 'other values'. It's not only facts that matter, but also the role of values in interpretations of these facts. Interviewees mentioned the following value-related issues:
 - Ethics: Should we assign similar value and similar rights to highly synthetic biological systems as we do to natural organisms?
 - Risks and benefits: How much risk is acceptable? Who will reap the benefits and who will bear the risks?
 - Can similar benefits be yielded with other means or strategies with less risks?
 - The impact of a shift from fossil-based to bio-based production processes, such as change in land use and impact on food supply.
 - Gaining public trust: The public is usually ambiguous, balancing between the hope that comes with innovations and science and the dangers. Both can be hyped and confuse the public.
 - Human genome editing: Possibilities for human germ line therapy raises a wide scope of ethical issues.

- Bio-piracy: Synthetic genomes do not come under the UN Nagoya protocol that dictates that any company using 'genetic resources' from one of the 95 parties that are bound by the protocol must negotiate an agreement on benefits and profit sharing.
- Who are the funders and what are their goals? Why funds US-DARPA more than 60% of risk research on gene drives, whereas the NSF program has not funded anything yet?
- **Safe by design:** Apart from the technical element –the potential of physical or biological containment measures- we should look at integrating safe by design principles at an early phase of innovation.
- **Education and raising awareness:** The scientists working on experiments with new biotechnologies should be the first to raise the alarm if something is potentially hazardous. Therefore, raising awareness and alertness for potential new risks among those scientists is urgent.

Although regulations may apply to new technologies and methods, this does not necessarily avoid citizens / DIYbiologists from experimenting with new biotechnologies and biological methods that are easy to access, low-cost and relatively easy to apply. Raising awareness that regulations apply and/or there may be potential risks involved is important. Europe could start educating the general public, students, medias and also governments.

- **International governance:** How does international governance deal with the transboundary aspects of rapidly emerging technologies such as gene drives which are designed to spread? In some countries experiments regulations require the highest containment level for experiments with gene drives as long as their effectiveness is not proven, but does that go for all countries?

Recently the AdHoc Technical Expert Group on synbio in the Cartagena Protocol on Biosafety has ceased. It was decided to continue the AHTEG on synbio in the Convention on Biological Diversity (CBD)⁴, which developed guidance on living modified organisms and insects and outlined what kind of aspects should be considered, with an open online forum. Some interviewees are worried that the sample of this forum will not be balanced, some countries that prefer to sustain business will put a lot of pressure to get rid of the current AHTEG synbio document and the outcomes will be biased.

- **'Dynamic governance':** There is a need for a governance model that fits to a rapidly changing world. Principles of what is called 'dynamic governance' have been applied in the nanotech debate and could be applied in synbio too. The process should be engaged, open and inclusive, i.e. with a clear role for stakeholders and the general public (for instance through science museums and local conversations) and it should allow for analysis and

⁴ The Cartagena Protocol is signed by 170 parties, which is not all members of the CBD (196 parties).

weighing of both benefits and risks. Consensus is not necessarily the objective, neither is polarization (a clash of extremes): It is more interesting to pick the shades of grey that can be found in justifications and normative considerations than the black & white of positions.

Taking the role of technologies in people's everyday life may be a good starting point for communication with publics.

- **Robustness, flexibility and responsiveness: a learning process:** The system should be robust, flexible and responsive to emerging technologies and the organizations generating data should be really independent. A few interviewees note that the experts often have an interest in experimenting with and applying technologies and there is usually few environmentalists or experts in ecology involved in Advisory Committees. Conflicts of interest should be avoided; Experts' Declarations of Interest help to create the necessary transparency.

Continuous reinterpretation of regulation as a result of changes in political winds should be avoided.

The need for adaptiveness goes for both the risk assessment methods and governance tools. We must build experience with such approaches by doing experiments.