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Responsible Research and Innovation in Synthetic Biology

Adaptive Biosafety Assessment as a Learning Process

Strategy Paper Annex 2: Workshop report

LIS Consult
February 24, 2017

Grant Agreement No: 321488

SYN-ENERGENE

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

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Adaptive Risk Assessment in Synthetic Biology – Workshop Report, Amsterdam, June 23, 2016

1. General introduction

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 1: Participant list)

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

2. Workshop introduction

The workshop began with an intro on the entire research project SYNENERGENE by Huib de Vriend (moderator). He spoke about the importance of mobilization mutual learning and by mutual learning (i.e. listening, understanding and responding). He presented the aims, the variety of stakeholders, and the focus on responsible research and innovation.

Therefore, the key questions are:

1) identify cases where risk assessments for genetically modified organisms fall short;

2) what are the adaptive strategies maintaining biosafety;

3) what is needed for the strategies;

4) identify actors and processes.

Then the participants were asked about their expectations of the workshop:

- to voice concrete steps and actions, getting get practical and empirical;
- dialogue, discussing issues such as trust, transparency, and to learn from mistakes;
- to see whether anything has changed since previous reports on synbio & safety and to define further steps;
- to look at the regulation, take a step back and rethink how we are assessing and managing risk;
- to identify what the roles are of different actors.

One of the participants emphasized that the term synthetic biology covers a large collection of very diverse technologies. There is a risk that discussing the risk issues of 'synthetic biology' is perceived in a broad and general sense. In the communication to the public at large this could create the impression that everything that has to do with synthetic biology is new and dangerous, which may trigger a general concern about everything that falls under the definition of synthetic biology. But in practice the risk assessment focuses on applications, not on a technology.

Participants agreed that current applications –for instance in enzyme production- and the vast majority of technologies and applications that is developing can be properly assessed with the tools provided by existing GMO regulation. It should therefore be emphasised that the risk discussion is about specific technologies and applications, although it is hard to carve that of, especially when you are dealing with a process-based regulatory regime.

3. Areas requiring more attention

Participants were invited to write 'areas requiring more attention', mainly concerns but also opportunities for safe design, on Post-Its and explain them for the group. This resulted in a list of 'areas of concern' that could be clustered while discussing them:

3.1. General principles of risk assessment and risk management

- **Protection goals**: We often lack clarity about what we want to protect;
- **Containment**: To what extend can organisms be really contained? The level of containment strongly relies on awareness and the behaviour of lab personnel working with engineered organisms.

Should we not worry about incidental escape because we can assume limited fitness of engineered organisms in general? 100% containment is virtually impossible, so what if one single escape can be fatal?

3.2. Inadequate knowledge and methods for proper assessment

- **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;
- **Longitudinal effects**, survival in evolutionary perspective;
- **Epigenetic effects**;
- **Germline modification and off-target effects**;
- **Gene drives**, meant for environmental release, is an area of concern that was mentioned by all participants. The effectiveness of localization strategies (i.e to keep the organism from spreading) is yet unknown;
- **Regulation of gene expression** was also mentioned by a number of participants and considered to be 'under the radar';
- **Minimal cells** which could make current risk assessment methods unsuitable because of the lack of a comparator;
- **Emerging properties** as a result of the introduction of new and complex (metabolic) pathways, and multiple modifications based on modularisation (biobricks);
- **Xenobiology**, either based on non-natural amino acids or non-natural DNA structures (backbone or nucleotides), and its impact on biodiversity.
- **Risk research lagging behind**: Risk research is not sufficiently rewarded, which is a major cause of risk research lagging behind with technological development;

3.3. Areas of application

- **Introductions in the environment (large scale),** e.g. modified algae and remediation;
- **Small-scale applications** in and around the house that are difficult to monitor and control, such as packaging with biosensors;

- **Rapid diffusion and low costs/easy access to the technology** (related to small-scale application).

3.4. Other topics

- 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 mammals[1] are developing. In the mean 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.

4. Needs

In the next step, the discussion was focused on needs, both in terms of knowledge and methods an in terms of organisation.

4.1. Knowledge and methods

- **Endpoints** have to be defined. What are the effects on environmental systems and effects on health that should be assessed? This has to start early because we need a baseline before we start applying new technologies of potential concern;

- **Advanced modelling** with the help of computer tools to process large data sets can add to the predictive value of risk assessment;

[1] 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)

- **Modularisation**: The principle of modularisation may also produce conceptual tools for risk assessment.

- **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[2]) 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[3].

    - 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]

- **New technologies as social experiments**: 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[5].

4.2. Governance issues

- **Public funding for risk research** that keeps pace with technological development;

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[2] Farren Isaacs is seeking a solution in multiple nutrient dependence on exotic amino acids. See: Rovner, A. J., Haimovich, A. D., Katz, S. R., Li, Z., Grome, M. W., Gassaway, B. M., … Isaacs, F. J. (2015). Recoded organisms engineered to depend on synthetic amino acids. *Nature*, *518*(7537), 89–93. http://doi.org/10.1038/nature14095

[3] See: Ostrov, Nili *et.al.* (2016). Design, synthesis, and testing toward a 57-codon genome. *Science* 9 Aug 2016: Vol. 353, Issue 6301, pp. 819-822. DOI: 10.1126/science.aaf3639

[4] Esvelt, Kevin M., Andrea L. Smidler, Flaminia Catteruccia, George M. Church (2014). Emerging Technology: Concerning RNA-guided gene drives for the alteration of wild populations. eLife 2014;3:e03401, http://dx.doi.org/10.7554/eLife.03401

[5] Van der Poel 's group at TU Delft started a research program "New Technologies as Social Experiments: Conditions for Morally Responsible Experimentation" in 2015:

- **Safe by design**: Apart from the technical element –the potential of physical of biological containment measures- we should look at the organisational element: what is needed to start this at an early phase of innovation.
- Because of the rapid diffusion of the technology we have to **facilitate pre-regulatory discussion in a non-official setting**. We need 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.

Adaptive Risk Assessment in Synthetic Biology –Workshop, 23 June 2016, List of participants

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