Adaptive Biosafety Assessment in synthetic biology

By Huib de Vriend*

One of the issues frequently popping up in debates about synthetic biology (synbio) is the possibility of introducing new and yet unknown types of biological risks. Both our unfamiliarity with undesirable impacts on health and environment and the high speed of development of new tools and applications raises the question how to apply Responsible Research & Innovation principles in biosafety assessment and risk governance procedures. This topic was addressed in several SYNENERGENE activities, such as a workshop and a number of interviews.

The biosafety of 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. Nonetheless, many experts recognize that the nature of innovative and emerging synbio technologies is uncertain[1]. Synthetic biology enables scientists to do experiments with biological systems that differ essentially from naturally occurring ones[2], which may no longer be the type of well-known and well-characterized organisms we have been dealing with so far.

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 or 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

1 SCENIHR (2014). Opinion on Synthetic Biology II – Risk assessment methodologies and safety aspects, Scientific Committee on Health and Environmental Risk, Scientific Committee on Emerging and Newly Identified Health Risks, Scientific Committee on Consumer Safety, European Commission.

2 Pauwels, Katia *et.al.* (2013). Event report: Synbio Workshop (Paris 2012) – Risk assessment challenges of Synthetic Biology, *Journal für Verbraucherschutz und Lebensmittelsicherheit*, September 2013, Volume 8, Issue 3, pp 215-226.

developments and a transparent, iterative process of risk governance, which includes risk assessment and dialogue among stakeholders including civil society globally[3].

A learning process

The challenge is to find ways in which developing knowledge, expertise and strategies needed for risk governance keeps pace with developments in synthetic biology research.

In SYNENERGENE this challenge is approached as a learning process that involves researchers, regulators, risk assessors, stakeholders as well as civil society. A dedicated SYNENERGENE workshop on June 23, 2016 and targeted interviews with experts and stakeholders in early 2017 elaborated on previous discussions and documents and focused on four key questions:

1. What are general considerations regarding the biosafety assessment of synbio technologies and applications;
2. What specific fields of technology (elements) and applications require attention;
3. What are the needs regarding risk research;
4. What are the needs in terms of risk governance?

Major synbio characteristics

Participants in the workshop and interviewees agreed on four major characteristics of synthetic biology with relevance to risk assessment issues:

1. Synthetic biology allows for a 'deeper level of engineering', changing and introducing more complex biological systems and traits;
2. Synthetic biology allows for introduction of entirely new (unnatural) biological and non-biological 'parts';
3. We are facing convergence of several sciences and technologies such as bioinformatics, high throughput technologies, DNA synthesis techniques and high precision modification techniques;
4. The costs of some of these technologies are decreasing rapidly and access to technologies is becoming easier.

Synthego, based in Redwood City, California, offers CRISPR gene editing kits and custom-built synthetic RNA in order to increase the speed and decrease the cost of genetic research.

[3] König H., D. Frank R. Heil, C.H. Coenen (2013). Synthetic genomes and synthetic biology applications between hopes and concerns. *Curr. Genomics* 14, 11-24.

New biosafety assessment issues

These characteristics have consequences in terms of complexity of biosafety assessment and the speed of development and diffusion of the technology, which raises several urgent risk governance issues.
Further deliberation on the consequences for risk assessment resulted in identified issues and considerations. Most participants and interviewees agreed that there is no need for reconsidering risk assessment principles for most technologies and applications. Nonetheless, they also mentioned several techniques and applications that require attention from a biosafety assessment point of view, such as gene drives, Xenobiology, gene editing of multiple genes or metabolic pathways and biosensors based on genetic circuits in medical applications. A few additional applications and fields of concern were mentioned by individual interviewees only, such as biohacking, de-extinction and engineering photosynthesis.

Workshop participants and interviewees also identified more specific risk issues:

1. The increased complexity and entirely new parts challenge the familiarity principle (lack of comparator);
2. Use of the biosphere for experiments: Introduction of entirely new traits in complex (eco-)systems challenges evaluation models which are often too simplistic;
3. Containment measures always have limits, especially regarding the ‚human factor' (lab regulations not properly applied, mistakes in construction of lab facilities), so we should ask ourselves: „How contained is containment?";
4. Rapid diffusion will lead to further increase of the number of applications, which creates work load problems for risk assessors;
5. We may be dealing with possible small scale applications at household level, which are far more difficult to monitor than current large scale applications;
6. Several participants have doubts about the effectiveness of technical safe by design approaches such as built-in localization mechanisms in gene drives.

From risk assessment to risk governance

Currently, risk research is already lagging behind. Rapid development and diffusion of the technology will increase the gap between innovation and our understanding of and hamper our ability to assess newly emerging risks. Moreover, these new technologies and applications may also require adapted regulation. The process of evaluating and eventually redesigning the regulation is notoriously slow, especially in Europe.

Both the participants in the workshop and interviewees identified scientific needs. Several methodological needs were defined, for instance the need for advanced modelling, techniques for analysis at system level (e.g. ~omics), developing containment strategies, and the need for facilities for safe experiments. Risk research policies should aim for multidisciplinary risk research integrated in (National, EU and international) innovation programs and making risk research more attractive to scientists: „We need a ‚Journal of failed experiments', one of the interviewees said.

In addition a number of governance needs was identified. The major needs are:

- Treat new technologies as social experiments, a process during which values, risks and benefits are identified, valued and monitored;
- Facilitate pre-regulatory discussion in a non-official setting;
- Integrate safe by design approaches at an early phase of innovation.

A social experiment as part of the learning process

Although the attitude of participants in the workshop and interviewees was very constructive, we observe several obstacles to treating new technologies as a social experiment. First of all, risk research has become a ‚*wicked problem*' in GMO debate, which makes scientists prone to criticism & debate-averse. A second obstacle is what could be called '*actors' regulation reflex*': Industry and Civil Society tend to focus on strategic position and regulatory issues rather than the social experiment. A third obstacle we observed regards the level of knowledge required to explore complex issues. This knowledge is not always available to all actors.

Technological innovation is a highly dynamic, usually non-linear learning process that calls for flexible and adaptive risk governance models if we really want to integrate safe by design approaches at an early phase of innovation. And although we have plenty tools at our disposal, there is no blueprint or tickbox methodology that tells us how to do this. The required flexibility and adaptiveness is only possible if innovation programs allow for learning by doing.

This article is based on an 'Adaptive Biosafety Assessment as a Learning Process – Strategy Paper' available at the SYNENERGENE website.

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