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Responsible Research and Innovation in Synthetic Biology

Adaptive Biosafety Assessment as a Learning Process

Strategy Paper Annex 1: Summary of interviews

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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

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Adaptive Risk Assessment in Synthetic Biology

Summary of interviews, January/February 2017

1. Definitions

No hard distinction

Several interviewees argue that there is no hard distinction 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. One of the interviewees distinguishes differences between the two based on quantitative and qualitative effects. Gene editing, for instance, can be applied to modify multiple genes (or their expression). It is a form of up-scaled genetic engineering that raises a magnitude issue. Examples of more qualitative are de-extinction and gene drives. In reviving de-extinct species you apply different technologies to do something that is quite different, in gene drives you combine molecular biology and population genetics.

Another interviewee defines synbio as an evolution in technology and methodology in terms of precision and targeting resulting in less random results and hazards and less 'waste' (more efficient use of inputs). Several interviewees refer to the standardization of parts that reflects the engineering approach that is typical for synbio.

Limited relevance of a definition for risk assessment

In the context of risk assessment definitions are relevant for legal reasons: those who experiment with and apply the technologies have to know what regulatory requirements they have to comply with. This is why in many fora, such as the UN AdHoc Technical Expert Group (AHTEG) on synthetic biology, a lot of time is spent on discussing and finding a consensus on definitions. NGOs argue that all novel techniques, such as CRISPR, should be regulated until they are proven to be safe. Although this is of importance, one of the interviewees notes that 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?

This brings us to the need for adaptiveness. We still have to do the assessments 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.

2. Areas that require attention

2.1. General considerations

- The old paradigm of biology that assumes causal relationships between genes and charateristics / behaviour of organisms is usually not valid while operating in complex systems such as the eco system and result in too simplistic models;
- One interviewee emphasizes that the current methodologies are still adequate to assess the risks of experiments and applications now and in the near future. However, in the long run we may get to introducing new risks;
- The speed of the technology developing makes it hard to keep up with risk research and regulation;
- Also 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.
- The interaction with the natural world is complex the models used to predict consequences have limitations;

2.2. Specific fields of application requiring 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 self limiting gene drives.

  One interviewee, however, argues 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** (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 charateristics.

- **Epigenetics and gene editing** is mentioned by three interviewees. There may be risks involved in changing the regulation of genes 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.
- One of the interviewees thinks that **biohacking** 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 favorable conditions for citizens science, also in biotechnology. In the US DIY labs provide opportunities both to ley 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 signaling systems,** for instance between plants and ecosystems, linked to gene switches that set a specific biomolecular reaction in motion.
- A topic only mentioned once by one of the NGOs is **de-extinction**. This NGO has serious doubts about claims for re-introduction of species that have extinguished. These species have usually extinguished because of loss of habitat. It's 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.
- **Xenobiology** (XNA and unnatural amino acids) makes it also difficult to compare with existing organisms

2.3. Specific elements requiring attention

- The **familiarity principle** is key in GMO risk assessment. Semi-synthetic host organisms may be so far off from natural organisms with a GRAS[1] status that it is no longer possible to use the **comparator** approach in risk assessment.

[1] GRAS = Generally Recognized as Safe

- New technologies allow us to **change more and different genes**, which also challenges the familiarity principle. We cannot simply say that the effect of multiple changes is the same as the sum of individual changes.
- **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. Needs

3.1. Needs regarding risk research

- **Defined by precaution**: 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.
- 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**.
- **Apply the case-by-case** approach: One interviewee doubts the necessity of complete understanding and prediction of everything and advocates 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 based on existing experience.

- **More experience**: There is e 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 have to 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.

- **Multidisciplinarity and integration in innovation programs**: Most interviewees notice that 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.

Several interviewees advocate 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 Manchester[2] and current plans at Wageningen University for integrating synthetic biology research, risk assessment and Responsible Research and Innovation could be inspiring examples.

3.2. Needs in terms of governance

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.

- **Integrated approach of normative issues**: Several interviewees argue that 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 rape the benefits and who will bare 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.

[2] http://synbiochem.co.uk/

- 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?

One interviewee mentioned dual use / bioterrorism: the increased risk of (intentional) abuse because the technologies become more accessible. Although the biosecurity issue is fundamentally different from the biosafety issue in terms of cause (intentional abuse vs. unintentional accidents) and safety measures, the type of hazard can be similar. Moreover, both issues are driven by the accessibility of technologies and methods and the two are often mixed in public debates. How to deal with this specific topic was not further discussed in this task of the SYNENERGENE project.

- **Make risk research 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**: One of the interviewees thinks the reponsibility for risk research should be put 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.
- **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.
- **Monitoring the field**: EFSA's Guidance on Post Market Environmental Monitoring of GMOs is an important tool to learn more about behavior and risks have to be implemented properly and systematically.
- **Capacity in risk assessment**: Both EFSA and national Adviory Committees and Competent Authorities have to handle an increasing number of applications under GMO regulation. A

solution has to be found for keeping up with legal time frames for evaluation while maintaining / improving the quality of the assessments.

- **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)[3], 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 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 have to build experience with such approaches by doing experiments.

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

3.3. Adaptive Risk Assessment in Synthetic Biology – List of interviewees

Name	**Affiliation**
Livoreil, Barbara	Fondation pour la Recherche sur la Biodiversité, France
Thomas, Jim	ETC Group, Canada
Kuzma, Jennifer	North Carolina State University, USA
Kuiken, Todd	North Carolina State University, USA
Pauwels, Katia	Biosafety and Biotechnology Service, Scientific Institute for Public Health, Belgium
Engelhard Margret	Bundesamt für Naturschutz, Germany
Sales, Louise	Friends of the Earth Australia
Martins dos Santos, Vitor	Chair for Systems and Synthetic Biology, Wageningen University, Netherlands