EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

Standing Committee for Life, Earth and Environmental Sciences (LESC)

ESF/LESC Strategic Workshop on

BIOLOGICAL CONTAINMENT OF SYNTHETIC MICROORGANISMS: SCIENCE AND POLICY

Heidelberg (Germany), 13-14 November 2012

Convened by:
Michele Garfinkel
European Molecular Biology Organization

SCIENTIFIC REPORT

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1. Executive summary

The workshop *Biological Containment of Synthetic Microorganisms: Science and Policy* took place at the evocative double-helix shaped Advanced Training Centre in Heidelberg, Germany, on the EMBL campus, from 13 to 14 November 2012. Fourteen external participants from 10 different countries participated in the workshop. Nigel Brown was the ESF observer. The format and the facilities of the seminar room permitted the efficient conduct of the workshop, and the space for coffee breaks just outside the room facilitated informal interactions and further discussions among the participants. Lunch on both days was at the new EMBL canteen, where the participants had further time for informal talks. The group was very enthusiastic and everyone participated actively in the discussions.

The aim of the workshop was to evaluate current knowledge and identify research needs in the area of biological (intrinsic) containment of synthetic microorganisms. Gaps in scientific understanding, areas in need of policy analysis, and the role of research adminstrators were emphasized. The workshop was structured so that scientific and policy aspects were discussed together in each session.

The first day focused on the interactions between microorganisms, both natural and genetically modified, and the environment, in particular on gene flow and its effects on the environment. The basic principles of risk assessment as it is carried out currently in Europe were presented and discussed. The most advanced scientific research on biological containment was presented, the feasibility of several different systems was discussed and research needs to improve these were identified. The formal talks for the day ended with a description of governance systems for biotechnology in general, and how these are now in flux partially as a result of the emergence of these new applications of biotechnology.

The second day, further scientific proposals to obtain biological containment were presented and discussed, followed by a discussion about whether synthetic organisms pose new risks to the environment compared to GMOs and organisms already found in nature. The actions taken at the European level to assess the research on and environmental risks of biological containment were presented, as well as current discussions at the international level within the Convention on Biological Diversity. The formal talks concluded with a discussion of the production of biofuels from microalgae, comparing the use of production mechanisms using genetically modified microorganisms with other technologies.

Key findings:

Needs or gaps were identified in a number of scientific research areas: requirements for biological containment, risk assessment of this containment, and incentives and rewards for research in those areas. Addressing these needs will require funders, scientific publishers, and research administrators to recognize these areas as important and to fund them.

An urgent need to further discuss the parameters of acceptable containment and, more important, what the process for achieving a decision on this would entail was also identified. This includes the definition of stakeholders, and who assesses the risk assessment, among other concerns.

2. Scientific content of the event

Eight talks were devoted to overviews of the science underlying the possibility of biological containment (sometimes called intrinsic biocontainment), and to descriptions of governance structures that could potentially support or interfere with the production of containable microorganisms that would eventually be used for the production of, e.g., biofuels, fine chemicals, pharmaceuticals, or nutrients.

Biological containment refers here to mechanisms that will stop the spread of microorganisms in an open environment. Auxotrophic bacteria that require the addition of specific compounds to grow are an example familiar from laboratories. However, a concern is that there will always be traces of the limiting compound available in the environment. Thus, constructing microbes that require the use of unnatural amino acids or unnatural nucleic acids may be preferred.

The framing questions for the workshop were:

- What are the environmental issues of concern?
- How can containment be achieved?
- How can a risk assessment for these new types of microorganisms be conducted?

The approach for the workshop was to use these talks and discussions to identify gaps in scientific knowledge as to how to make biological containment work, complemented by identifying potential problems in governance structures (including risk analysis) that could make difficult the evaluation of new, biologically-containable microbes.

A recurring theme in the talks and discussions was how to use the understanding of risk in a way that helps policymakers in their tasks. Specifically, the point of risk assessment and risk mitigation is “to protect things that should not be harmed”, as one workshop participant said. How do risk regulators decide what those “things” are? Is this any harm, or only irreversible harms?

A related theme was to think about how to define how much containment is necessary to allow the release of a microbe to be called “safe”. Is this absolute? Under what conditions is gene flow allowable?

In all discussions about “risk” and “safety”, inevitably, and rightfully, the next question is “who decides?” Several of the talks addressed this important governance issue from the point of view of scientists, regulators, and environmentalists.

Many of the discussions were focused on synthetic biology, although synthetic biology per se was not the focus of the workshop.

Geoff Squire – Gene flow and ecological systems

Dr. Squire gave an overview of the European Food Safety Authority guidelines for the environmental risk assessment of genetically modified organisms. The guidelines were last revised in 2010, a process to which he was a contributor. He summarised areas of the guidelines that still need further refinement or development, particularly as they may be applied to synthetic organisms. In particular, the central notion of "familiarity" with an existing organism; the lack of consideration of the entire ecosystem; and the need to include an assessment of the benefits and trade-offs may be missing in the types of evaluations that EFSA can carry out.

Discussion: Dr. Squire's talk set up the key points for discussion for the remainder of the meeting. Concerns that were raised by him and by the other participants for attention included gene flow (namely: gene flow does happen, what does that mean for containment and risk assessment?), risk assessment without prior comparators, and risk assessment starting from a system analysis rather than a gene analysis. Participants generally agreed that starting from a system view rather than a gene view is preferable, but how to carry out such an assessment will require more research and practice by risk assessors.

Radha Krishnakumar – Intrinsic biocontainment of engineered and synthetic organisms

Dr. Krishnakumar introduced the technologies of synthetic biology and synthetic genomics, describing the approach used at the J. Craig Venter Institute to construct a synthetic cell. She then described her research aimed at creating orthogonal biological systems with the capacity to use more than the standard 20 amino acids. This approach would produce microorganisms that are intrinsically biocontained (i.e., the building blocks they need to grow and reproduce are must be provided and cannot in general be found in nature).

She noted that this type of research is not rewarded in the ways other important basic research is (e.g., with grants, publication in top journals, and in evaluations for tenure) and thus both how this research is thought of and what sources of money might fund it must be thought about more deeply.

Discussion: Beside the useful detail on orthogonal biology provided by Dr. Krishnakumar, her talk advanced discussion of the general concepts of evolutionary stability and the degree of containment needed depending on how stable or unstable a microorganism might be in the environment. The main discussion stemming from this was whether it is worth differentiating natural, modified, and synthetic organisms from a risk assessment perspective. The general sense from the participants was that there is no evidence yet that classes of risk will vary between these three types of organisms, but that not enough risk research has been done to fully understand this.

There was a suggestion that general principles may be applicable for the release of any organism (microbe, plant animal); not all of the participants agreed with this idea.

Further, Dr. Krishnakumar had pointed out that these concerns are discussed in the community of scientists carrying out both research on biological containment using orthogonal systems, and scientists who intend to use those systems to contain their constructed microbes.

Victor de Lorenzo – Refactored bacteria on the loose: something old, something new

Dr. de Lorenzo's talk focused on synthetic microorganisms that would need to be released into the environment to perform their functions, for example, to clean polluted soil and water or to degrade industrial waste and to detect explosives in the ground. He explained that the environmental risks posed by bacteria created in the lab have been largely studied already, and these risks are low because engineered bacteria are much weaker than their natural counterparts, and when released in the open, are quickly destroyed. However, new academic research is needed to assess the environmental risks posed by synthetic engineerd microorganisms based on *non-familiar* biochemistry (e.g., of the sort that Dr. Krishnakumar discussed earlier).

Discussion: A major concern of the participants following this talk was whether various environmental release studies were done on intentionally or accidentally released microorganisms. Both Europe and the United States have useful data on intentionally released microoganisms (in field trials) but some participants did say that it would not matter if the releases were intentional or accidental with respect to interpreting data, while others did think this difference matters.

The other major issue, which had come up at least tangentially in the two previous talks, is what sort of assessments needs to be done for the release of microbes constructed using non-familliar biochemistry (alternative nucleic acids or amino acids) v. familiar biochemistry (novel sequences, but using natural nucleic acids or amino acids). It was generally agreed that more academic research is needed to assess environmental risks presented by the former. There was some disagreement as to whether more research was needed on the latter, but generally it was thought that the construction of microbes of novel sequence with familiar biochemistry would fall solidly into current approaches to risk assessment.

Joyce Tait – Governance: an area of flux

Dr. Tait explained the limitations of the current governance of genetic engineering and biotechnology in Europe, in particular the bottom-up approach involving a wide range of stakeholders in the decision making process, which in some cases has caused the disregard of scientific evidence in the effort to accommodate all opinions. She suggested that downstream governance of biotechnology needs to be more flexible and adaptive to the opportunities brought about by new scientific discoveries, to enable decision making to be based more on scientific evidence and less on public opinion.

Discussion: There was general agreement about the need for flexible, adaptive governance. How to achieve this remains open to discussion and it was suggested by some participants that this would require "governance experiments". What those would look like could be the subject of another inquiry.

Dr. Tait had additionally pointed out that provisions within the Convention on Biological Diversity's Cartagena Protocol (on biosafety) have had an inhibitory effect on research and innovation related to GMOs, including on ways to mitigate any potential hazards of GMOs in the environment (i.e., has inhibited biological containment research).

Markus Schmidt – Xenobiology

Dr Schmidt explained that xenobiology is the construction of orthogonal biological systems based, for example, on polynucleotides different from the naturally occurring DNA and RNA, called XNA (xenonucleic acid). Having a different biochemistry, these new systems can be used to build a biological containment that is expected to have no genetic interactions with natural organisms, and therefore be safe in terms of horizontal gene flow. Only a few research groups are currently working on xenobiology, and more scientific research is needed, as well as policy work, to assess the benefits and risks of these non-canonical life forms.

Discussion: In his talk Dr. Schmidt had proposed that a xenobiology approach would be the best biosafety tool possible, as these would be firewalled from the natural (current) world. There was significant discussion about this, both about the premise, and what needed to be done if the premise were as safe as predicted. On the premise itself, the challenge seems to be, how do we determine that a firewall exists and will hold? This will require academic and field research (i.e., some type of experiment outside of the laboratory) to determine if the premise is correct. If the premise turns out to be true, does this also mean there would be public acceptance of the use of the microorganisms in an uncontained setting? That has been unclear up until now, and remained so among the participants. Sometimes, technical fixes do lead to better public acceptance, sometimes they do not. "Safety by design" is an important concept especially in industrial settings that is not used as frequently as it could be in other settings.

The issue of familiarity came up here as well, with the concern that something that seems unfamililar may be looked upon more negatively than something that is familiar, even if the unfamiliar thing is in fact safer for the environment. Understanding (and where relevant, resolving) this disconnect would likely benefit from social science and communications research.

Ioannis Economidis – Does the emerging role of synthetic biology in biotechnology imply new risks?

Dr Economidis summarized all mechanisms implemented by the European Commission to discuss and fund the science and the ethical aspects of synthetic biology. He explained that synthetic biology has an important role in the creation of a European Knowledge-Based Bio-Economy (referred to as KBBE in Framework Programme 7). He added that the negotiations for Horizon 2020 are still ongoing, but synthetic biology is already included as a tool to foster European industrial innovation. His view is that synthetic biology does not indicate new risks compared to genetic engineering; therefore, the tools developed to assess the risk of GMOs could be used also for synthetic organisms.

Discussion: The intersection between the emerging bioeconomy and governance, regulation, and societal concerns is being explored in a number of arenas. The specific intersection with risk assessment and risk mitigation is a particularly interesting one, and remains under-explored. A key question emerging is what risk analysis tools need to be in place in order to not disrupt the emergence of new biotechnology products, while still assuring safety (in the common-sense way). This issue was taken up again in the more general discussion, and will be an important problem for follow-up.

Adrian Peres – Synthetic biology and the Convention on Biological Diversity
Dr. Peres provided an overview of the Convention on Biological Diversity, focusing on Decision XI/11 ("new and emerging issues relating to the conservation and sustainable use of biodiversity") in relation to Decision IX/29 ("operations of the Convention") of the respective Conferences of the Parties.

Sammy Boussiba – Microalgal biotechnology and the sustainable development of biofuels

Dr. Boussiba illustrated the process to obtain biofuels using microalgae, and concluded that although algal biofuels were a promising and attractive alternative to fossil biofuels, research done so far has shown that they are not sustainable because of their high production costs. He then presented other more feasible uses of genetically modified/synthetic microalgae to produce value-added products, such as carotenoids and nutritional supplements.

Discussion: The presentation by Dr. Boussiba precipitated discussion about whether biofuels are worth pursuing, with or without genetic modification, and a more general discussion about expertise (tying in some with Dr. Tait's talk on governance). With regard to biofuels, it is clear that with current costs for the production of standard fuels and new sources being developed, biofuels will not be competitive only on price. More important, they are unsustainable under current production methods. The question then is whether genetic engineering will change this situation; this needs much more research (scientific and economic).

3. Assessment of the results, contribution to the future direction of the field, outcome

Science

The need for funding and mechanisms to support **research on biological containment** was identified or agreed to as a critical gap by all participants. This type of research tends to fall outside of classical funding schemes: it is not thought to be novel enough for funders such as the European Research Council or the National Institutes of Health, but at the same time it is not close enough to a product to qualify for industrial funding schemes. It may be that private firms are indeed working on this as part of their overall businesses but there is no way for us to know that at the moment.

Further, the individual scientists carrying out this type of research seem to have some sense that this research is not valued and may even count against them in terms of future funding, publishing, and tenure decisions. Grants, publishing, and tenure are thought of as rewards for good research, but they can also be used as **incentives for research** (especially grants). This gap, and how to incentivize and reward biocontainment research needs to be discussed further at least between scientists and funders, especially at the government level.

Similarly, whether risk assessment models as they stand will be able to accommodate these new organisms must be considered and may require **new risk assessment research**. As our understanding of non-familiarity and novelty become more sophisticated, we may come to an understanding that what is needed is **risk assessment without comparators.** The view might be extended to include a system-based risk assessment, and the explicit inclusion of trade-offs in the risk assessment (including the risks of doing nothing).

Policy

What is the added value of biological containment? If industrial microbiology could be carried out at a level that scale-up could be limited to contained growth (i.e., in a closed vessel) then most of this discussion would be unnecessary. But industrial process for biofuels, animal feeds, or certain chemicals can only usefully be carried out by scaling up exponentially from contained growth. The implication is that such scale-up would need to occur outside the laboratory.

Additionally, even for work contained within a laboratory, there may be a need for an additional level of biological containment in the event of an escape from the laboratory (related to the concept of “safety by design” discussed above).

Biological containment may thus have also some influence on public acceptance of these technologies, especially when coupled with physical containment. A technical approach like this coupled with using scientific evidence more than consensus while still involving non-science stakeholders may make upstream acceptance more likely, and flexible downstream governance more acceptable.

The question of “what should scientists do?” came up frequently though generally in an oblique way. Participants viewed the possible **roles of scientists** as including not only their research expertise, but as leaders to help the public come to reasoned decisions. Following a structured discussion, they also saw the role of scientists as being able to influence other scientists who are in administrative roles to, for example, fund biocontainment research.

Critically, it was noted that from policymakers’ perspectives, while there seem to be many avenues for hearing about risks, there are far fewer ways to hear about potential benefits in very detailed and specific, but still understandable, ways. Policymakers are more likely to embrace some risk if the potential benefit is clear, even if it is not assured. This seemed to be especially true for human health, but also to a degree for environmental remediation.

However, the general sense of the participants was that the discussion of benefits has been missing because scientists have been missing from those disucssions. This is somewhat in

contradiction to another perception of scientists: that they are only focused on benefits. Learning what policymakers actually perceive and need for their work would be critical for reconciling these two views.

Government/governance/communication The overall discussion about the interaction of scientists, the public as a whole, and policymakers was quite sophisticated. There was an agreed sense that “public education” or even “public understanding” is not what we are really trying to get to. Rather, ideas such as “design for X” (in this case, “design for safety”) capture and address concerns of the public and policymakers, including scientific administrators, and thus are constructive ways to move toward better governance discussions that can address the trade-offs needed to achieve a particular application or benefit.

On expertise (related to the “who decides” problem), there was general agreement that it is helpful to start by arguing from the science, but that decisions are never made solely on the science. The question then is what additional factors should be accounted for, and who the stakeholders in such a process are. “The public” in general did not seem to be the right answer, but neither did individual experts. This is more about a process than an individual opinion, and almost certainly would require an interdisciplinary group.

Follow-up ideas and plans:

Many of the participants thought that it would be worthwhile to try to form a COST-funded network to continue to discuss and expand this work, and strengthen the interactions between those focused on science and those focused on governance. Discussions with participants and potential additional members are ongoing. The most important additional stakeholders to add in such a network would be from environmental sciences and from environmental non-governmental organisations, sectors that were underrepresented at the workshop. Additionally, if possible, funders would also be included in such a network.

The need for funding and mechanisms to promote research on biological containment systems was identified as critical for scientists, risk assessors, and policymakers to be able to carry out work or make decisions about the safety and use of synthetic (or highly-modIfied) microorganisms. The Convenor of this workshop as well as several other individuals would like to convene another workshop on this particular issue that would serve to generate specific options and potentially recommendations for governmental and non-governmental funders, and would bring together funders, scientists, policymakers, environmental experts, and other stakeholders.

We (the Convenor and other EMBO staff) as part of our usual work would like also to expand on this report to be able to offer more background information on this topic to scientists, funders, and policymakers generally. Other participants expressed interest in this type of work and we would of course include them in drafting any expanded report.

Many of the workshop participants are involved in various groups or committees working on related issues, and will be able to discuss the findings of this workshop, and any additional work, in relevant forums.

4. Final programme

Tuesday, 13 November, 2012

09.00-09.20	**Welcome by Convenor** **Michele Garfinkel** European Molecular Biology Organization, Heidelberg, Germany
09.20-09.40	**Presentation of the European Science Foundation (ESF)** **Nigel Brown** ESF Standing Committee for Life, Earth and Environmental Sciences (LESC)
09.40-12.30	**Morning Session: Ecology and new technologies**
09.40-10.40	**Gene flow and ecological systems** **Geoff Squire** (James Hutton Institute, UK)
10.40-11.10	*Coffee / Tea Break*
11.10-12.00	**Synthetic cells and biological containment** **Radha Krishnakumar** (J. Craig Venter Institute, United States)
12.00-12.30	**Discussion**
12.30-14.00	*Lunch*
14.00-17.45	**Afternoon Session: Synthetic Biology, microbes, and the environment**
14.00-15.00	**Refactored bacteria on the loose: something old, something new** **Victor de Lorenzo** (CSIC, Madrid, Spain)
15.00-16.00	**Governance: an area in flux** **Joyce Tait** (INNOGEN UK)
16.00-16.30	*Coffee / tea break*
16.30-17.45	**Discussion**
17.45-18.00	**PREPARATION FOR NEXT DAY**
19.00	*Dinner at Akademie*

Wednesday, 14 November, 2012

09.00-12.15	**Risk assessment**
09.00-09.45	**Xenobiology** **Markus Schmidt** (Biofaction KG, Vienna, Austria)
09.45-10.30	**Does the emerging role of synthetic biology in biotechnology imply new risks?** **Ioannis Economidis** (Brussels, Belgium)
10.30-11.00	*Coffee / Tea Break*
11.00-12.15	**Discussion**
12.15-13.45	*Lunch*
13.45-15.45	**Afternoon Session: Biofuels**
13.45-14.00	**Synthetic biology and the Convention on Biological Diversity** **Adrian Peres** (DG Research and Innovation, EC, Brussels, Belgium)
14.00-14.45	**Microalgal biotechnology and the sustainable development of biofuels** **Sammy Boussiba** (Ben-Gurion University of the Negev, Israel)
14.45-15.45	**Discussion**
15.45-16.00	*Coffee / Tea Break*
16.00-16.30	**DISCUSSION ON FOLLOW-UP ACTIVITIES/NETWORKING/COLLABORATION**
16.30	*End of Workshop and departure*

5. Final list of participants

1. **Sammy BOUSSIBA,** Ben Gurion University of the Negev, Israel
2. **Victor DE LORENZO**, National Center of Biotechnology, Madrid, Spain
3. **Ioannis ECONOMIDIS**, Indipendent Scholar, Brussels, Belgium
4. **Franco FURGER**, Netlandscapes, Luzern, Switzerland
5. **Sibylle GAISSER**, Hochschule Ansbach, Ansbach, Germany
6. **Lieve HERMAN,** Instituut voor Landbouw-en Visserijonderzoek-ILVO, Melle, Belgium
7. **Rodica-Mariana ION,** National Institute of Research and Development for Chemistry and Petrochemistry, Bucharest, Romania
8. **Radha KRISHNAKUMAR,** J. Craig Venter Institute, Rockville, USA
9. **Adrian PERES**, European Commission, DG Research and Innovation, Brussels, Begium
10. **Thomas REISS,** Fraunhofer ISI, Karlsruhe, Germany
11. **Markus SCHMIDT**, Biofaction KG, Vienna, Austria
12. **Geoff SQUIRE,** James Hutton Institute, Edinburgh, UK
13. **Dirk STEMERDING**, Rathenau Institute, The Hague, The Netherlands
14. **Joyce TAIT**, Innogen, University of Edinburgh, Edinburgh UK

One additional person on the original participant list (from France) needed to cancel travel the day before due to an urgent situation.

ESF Representative

15. **Nigel Brown,** The University of Edinburgh, Edinburgh, UK

Convenor

16. **Michele Garfinkel**, EMBO Science Policy Programme, Heidelberg, Germany

Local Organiser

17. **Sandra Bendiscioli**, EMBO Science Policy Programme, Heidelberg, Germany

6. Statistical information on participants

Age bracket	No of participants	%
30-40	2	14%
40-50	5	36%
50-60	4	28,5%
60-70	3	21,5%
Gender distribution		
Female	5	36%
Male	9	64%
Country of Origin		
Austria	1	7%
Belgium	3	21,5%
Germany	2	14,3%
Israel	1	7%
Netherlands	1	7%
Romania	1	7%
Spain	1	7%
Switzerland	1	7%
United Kingdom	2	14,3%
United States	1	7%