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Synthetic Biology

Submission to the CBD

With Decision IX/29, and in particular in accordance with paragraph 4 of decision X/13, the CBD called for "submissions of information on synthetic biology and geo-engineering, while applying the precautionary approach to the field release of synthetic life, cell or genome into the environment".

We herewith would like to submit our concerns and relevant information to particular aspects of Synthetic Biology, such as DIY Synthetic Biology and Bio-hacking.

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1 Synthetic Biology is already underway

Synthetic Biology and the development of Synthetic organisms (Synthetic LMOs /GMOs) need urgent attention from the SBSTTA because it is already underway, but largely without regulation or risk assessment. This depends also - but not only - on the question how related risk technologies such as genetic engineering are regulated in the individual countries.

There are at least four different areas in which Synthetic Biology and the development of Synthetic GMOs are taking place: commercially, scientifically, as competitions for undergraduates and as garage biotechnology, an by suppliers of synthetic DNA and compounds.

1.1 On a commercial level

Synthetic Biology is being developed and applied by an increasing number of companies that mainly aim for the production of bio-based materials and agrofuels. Their projects aim for large, global markets, and due to the high incentives to replace declining fossil fuel supplies, large scale adoption in a short time frame must be expected. Beside microbes, field crops and trees these include work on algae for agrofuel. This has also been described as “extreme genetic engineering”.

> “Synthetically-constructed organisms are already employed in the production of thousands of tonnes of biofuels and biobased chemicals, far in advance of research or debate about their safety and efficacy or about the assumptions underlying the techniques involved.”[1]

1.2 On a scientific level

In the scientific area, several groups work on the development of different types of Synthetic organisms.[2] Scientific institutes such as the Massachusetts Institute of Technology (MIT) are also involved in projects including a competition for undergraduates and high-school students called the ‘international Genetically Engineered Machines’ competition (iGEM).[3] This targets undergraduates and high-school students to get them engaged in the construction of Synthetic organisms (Synthetic GMOs). iGEM provides infrastructure, several thousand synthetic DNA sequences and organisms such as *E. coli* and yeasts through the ‘Registry of Standard Biological Parts’[4] and in cooperation with the non-profit BioBricks Foundation.[5]

In June 2011, Defense Advanced Research Projects Agency (DARPA) of the US Defense Department, started the Living Foundries program, to “support academic and corporate researchers for developing and applying an engineering framework to biology for biomanufacturing.” The goal is to "break open the field to new players so [they] will not have to be experienced in genetics to design new biological systems."[6]

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1 ETC Group (2010): The new biomassters.

2 Gibson D. et al (2010)

3 http://www.igem.org/

4 http://partsregistry.org/Main_Page

5 http://biobricks.org/

6 Pennisi E. (2011): DARPA to Offer $30 Million to Jump-Start Cellular Factories; Science Magazine, 29 June 2011.

1.3 As garage-biotechnology – DIY biology

Synthetic Biology is also done by self-described 'bio-hackers', as DIY biology (also known as 'garage biotech'), as well as games and competitions for school and university students. The numbers of people engaged in this can only be guessed, since in a lot of countries there is either no registration and regulation for such laboratories, or authorities have little opportunity to regulate. Communication does not take place in scientific journals, but largely on blogs, (anonymous) websites and mailing lists, in set-ups similar to the computer hacker spaces.

See for example DIYbio[7] that describes itself as "an Institution for the Amateur Biologist". DIY Bio claims to have an informal network of over 2000 DIY synthetic biologists and students and its website features a map of DIY chapters and contacts that includes individuals and groups in Australia, Brazil, Canada, Columbia, India, Japan, Mexico, Solomon Islands, Switzerland, Thailand, USA and several EU member countries. Among other things the website announces local groups and meet-ups[8] as well as hands-on courses in genetic engineering for 300 USD,[9] but operates anonymously.

This type of "garage biotechnology" often employs used or hacked equipment. Special efforts are underway to develop cheap equipment such as PCR machines that can be connected to normal laptops (see for example http://openpcr.org/). However such efforts do not seem to include appropriate hacks for waste disposal.

1.4 By suppliers

An increasing number of suppliers for Synthetic DNA operate worldwide. In 2007, the ETC Group listed 66 of them, mainly in North America, Europe, Asia, but also in countries like Russia, South Africa and Iran.[10] It is likely that this number has increased since then.

Some of these companies not only supply the Synthetic DNA but also insert them into vectors (e.g. bacterial, mammalian and yeast cells) and plasmids ready for engineering into organisms and then deliver them to their customers.[11] A specialized synthetic biology company such as Ginko Bioworks further contracts with larger firms to design and engineer synthetic organism to specification for use in industrial processes.[12]

There are no strict regulations to indicate who is responsible for risk assessments in these cases. While there have been voluntary codes developed which commit some gene synthesis companies and US NIH grant

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7 http://diybio.org/

8 http://diybio.org/local

9 "Genspace is repeating its popular Biotech Crash Course starting Sunday March 20th. It will run from 2PM to 6PM on three consecutive Sundays and cover all the basic techniques used to cut and manipulate DNA. This is a hands-on course where you will isolate DNA, cut it using restriction enzymes, amplify it using PCR, and clone it into bacteria. The cost for the course is $300. We have 12 slots available, with two at a special discounted student rate." http://diybio.org/blog/biotech-crash-course

10 ETC Group (2007): *Extreme Genetic Engineering.* Report. Map of Commerical DNA Synthesis Companies, p. 8-9. The companies were located in the USA & Canada, Europe, Russia, India, China, Korea, Taiwan, Japan, Australia, South Africa and Iran.

11 See for example service provided by synthetic gene providor DNA 2.0 marketed as "any sequence in any vector" - https://www.dna20.com/index.php?pageID=303

12 Ginko Bioworks: http://ginkgobioworks.com/works.html

recipients to check the requested sequences against databases of sequences of known pathogens and toxins,[13] such codes have no legal enforcement. Given the international spread of Synthetic DNA suppliers it would be impossible to get all companies to act under strict and binding regulations. This leads to a situation where any DNA sequence that has ever been published can be used to recreate known pathogens or to create new ones, both intentionally and unintentionally. Politically this is often only discussed as a threat of bio-terrorism against humans, but it would be equally possible to produce plant and animal pathogens this way.

The question of risk assessment becomes even more relevant for companies that deliver Synthetic GMOs and vectors on customer demand. Who could even be responsible for a risk assessment? The producing company that just fulfils an order, or the customer who never even had the Synthetic organism in their hand?

This lack of risk assessments combined with a worldwide commercial network can pose serious threats to biodiversity, and may constitute a breach of the Cartagena Protocol.

2 Synthetic Biology affects the attainment of the Convention and its Protocols

The Convention on Biological Diversity has long since accepted that genetic engineering, specifically Living Modified Organisms (LMOs) can have a negative impact on biodiversity. This has resulted in a number of decisions, e.g. on genetically modified trees, and in the approval of the Cartagena Protocol on Biosafety. An AHTEG has been working on developing new guidelines for risk assessment and risk management of specific LMO/GMO categories, such as GM mosquitoes GM trees, and stacked genes.

Some of the Synthetic organisms that are currently proposed, developed or in early stages of commercialisation are actually genetically modified organisms, or rather 'living modified organisms', for example Synthetic GM algae for biofuel production, Synthetic GM plants with changed composition or additional enzymes for more effective biomass production, or Synthetic GM bacteria and yeasts for the production of compounds for industrial processing. The concerns raised about LMOs under the CBD and the Cartagena Protocol are even more pertinent for Synthetic organisms than they are for current GM crops utilising single genes acquired from bacteria.

Where Synthetic Biology relies on genetic information and DNA sequences it also targets the Nagoya Protocol on Access and Benefit Sharing. It also raises additional questions about how genetic information can be recorded and virtually transported without the actual material ever being taken out of its originating area. When genetic information becomes 'just' DNA sequences in a database, easily reproducible with synthesizers, then it will become increasingly difficult for countries, indigenous peoples and local communities to prove that the information originated from them.

Synthetic Biology is a new and emerging issue that is relevant to the attainment of the objectives of the

13 Ideas of self-regulation and possibly boycotting companies that would not check the DNA sequences ordered from them, were discussed but not implemented. See for example the report of IASB (2008): Technical solutions for biosecurity in synthetic biology Munich, 2008; or Schmidt M. (2008): *Diffusion of synthetic biology: a challenge to biosafety*. Systems and Synthetic Biology 2: 1–6.

CBD, its work programmes and cross-cutting issues, and it poses a risk for the conservation and sustainable use of biodiversity. Based on the current R&D projects and on early examples of commercialisations, Synthetic Biology is relevant to the following work programmes: agricultural, dry and sub-humid land, forest, inland waters, island, and marine and coastal biodiversities. It also has effects on a number of cross-cutting issues: sustainable use of biodiversity, biodiversity for development, climate change and biodiversity, ecosystem approach, invasive alien species, technology transfer and cooperation, and article 8(j) on traditional knowledge, innovations and practices.

Civil society organisations have highlighted the risks repeatedly over the years.[14] For this submission we would like to concentrate on a few issues:

- the lacking basis for risk assessments of Synthetic organisms,
- Synthetic biology and waste, and
- the lax approach to Synbio in the DIY space.

3 Lacking basis for risk assessments of Synthetic organisms

Synthetic organisms are different from LMOs in a number of issues: the sheer number of DNA fragments inserted, the synthetic origin of these sequences that are not copies or even 'reproductions' of existing DNA but are novel, the removal of large portions - or even all - of the original, natural DNA from the modified organism or the aim to not 'improve' an existing organism, but to develop a new one that by definition does *not* come with the traits of the natural one.[15]

Depending on where it is done, current risk assessment of GMOs is often largely based on assumptions of substantial equivalence, familiarity or prior experience with the receiving organisms, the intended new GM trait and similar GMOs.[16]

Whilst this approach is widely criticised, such assumptions would be highly inappropriate for Synthetic GMOs. For example the use of high numbers of introduced synthetic DNA sequences makes it impossible to attempt to simply add up their possible effects, since they can influence each other and the resulting phenotype in numerous ways.

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14 E.g. two reports by the ETC Group *Extreme Genetic Engineering: An introduction to Synthetic Biology* (2007) and *The new BioMassters* (2010), ETC (2010): *Briefing and Recommendation for Delegates ot CBD COP10 in Nagoya.* http://www.etcgroup.org/en/node/5201, or EcoNexus (2010): *Synthetic Biology. Letter to the New Scientist.* New Scientiest, Issue 2772, p.24-25, 7 August 2010.

15 Two examples: (1):"Synthetic yeast designed by Amyris Biotechnologies, which is about to be used commercially on a large scale in Brazil, has additional DNA constructed from 12 synthetic genes taken mostly from plants but all slightly altered to work in a particular microbe." (2) Christopher Voigt form the University of California (San Francisco has developed Bio-MeX, a 'feedstock-flexible' method through which Synthetic GM microbes with 89 new DNA sequences can break down otherwise unprocessed plant material. From ETC (2010): The New BioMassters; (1) footnote 175, (2) footnote 184

16 Already for GMOs this approach is often seen as in-sufficient, and over the years additional issues have been included into the environmental risk assessments, e.g. effects of Bt toxins on non-target organisms, effects on the soil, contamination of other crop varieties etc.

In many cases, the explicit goal of Synthetic Biology is to produce organisms with as little similarity as possible to the original species on which they were based. A risk assessment of a Synthetic GMO therefore needs to cover as a start all the areas that would be covered for a GMO - but without any of the notions of familiarity and prior knowledge.

At the moment the discussion of what is a sufficient or appropriate risk assessment for a GM crop is still ongoing. For other organisms such as GM trees or GM insects there are not even tentative agreements or cases to which one could refer. GM algae do not even appear to have been discussed so far. If these questions have not been solved for GMOs, then there is no basis for assessing the more far-reaching cases of Synthetic biology and extreme genetic engineering.

4 Synthetic Biology and Waste

4.1 Release of Synthetic GM microbes through waste and sludge

Waste from industrial processes based on biomass and from fermenters are already now used as fertilizers and as animal feed. Selling waste products instead of paying for their disposal makes economic sense and it is obvious that such practice will not stop just because Synthetic GM microbes are involved.

> "The case is relevant to the use of synthetic organisms in commercial biorefineries, which will also produce waste residues for disposal. Moreover, such biorefineries are not currently expected to put in place very stringent biosafety procedures, acting more as industrial brewing facilities than high-tech laboratories. Indeed evidence from the beer brewing industry that uses yeast for fermentation, just as existing commercial synthetic biology refineries do, suggests that escape of organisms may in fact prove quite common. According to brewing expert Hugh Dunn, a study involving six breweries investigated over three years discovered that commercial strains of cultured yeast do escape into the environment. Biodynamic vineyards have already raised concern that even non-engineered escaped strains could impact the flavour and character of their wines.[17]

4.2 The value of waste

Synthetic Biology and so-called ‘next-generation agrofuels’ regard a lot of plant material as low-value or even as waste. This ranges from ‘low-value forests’ (e.g. mixed forest, shrubby trees etc) to ‘agricultural waste’ such as straw, leaves or branches. The language of Synthetic Biology denies both the current use of these plant material (e.g. straw in animal rearing) and their ecological functions, e.g. it as shelter for insects and other animals in winter. Plant materials are also “important components of soil recycling of nutrients and its capacity to sustain biodiversity and crops, absorbing CO_2 and water (FoE 2010).

Attempts to use Synthetic GM microbes built to break down any type of biomass, mean that any source of biomass becomes a commodity that can be turned into highly priced fuel. When Synthetic Biology leads to whole plants being totally taken off the fields with nothing left behind, then it neglects to take into account

17 ETC (2010): The new BioMassters.

that even field crops are part of ecosystems and that crop plants have different uses in nutrient cycling and for different systems and different people.

We already now have the problem that where biomass extraction leaves fields bare, it destroys soil fertility, adversely effecting biodiversity and endangering the ability of farmers to live off the land. This situation is likely to continue with Synthetic organisms for biomass production.

By developing Synthetic organisms that can uses biomass to produce a range of different compounds for further processing, agriculture on large scales can be reduced to just growing those biomass plants, be it sugar cane, maize etc. This will further reduce agricultural bodiversity.

Already now, the increasing concentration of farmers to cultivate maize for ethanol production instead of other crops shows adverse effects on birds in agricultural landscapes since ground-breeding birds loose habitats to do so.[18]

5 DIY - Treating Synthetic Biology as a game – The hacker sphere

In contrast to the genetic engineering undertaken at research institutions and companies, Synthetic Biology is also undertaken by a different set of actors at very different locations and premises.

Particularly in countries with little regulation of genetic engineering laboratories, (extreme) genetic engineering and Synthetic Biology now take place in private houses, schools and hacker spaces. Annual competitions, school and university challenges replace scientific publications and commercialisation processes and assessments. Recognition by peers in blog postings and through (anonymous) websites replaces review by the scientific community.

Traditional approaches to the regulation of work places (including safety issues) and products cannot provide any risk assessment in such settings. The risks for biodiversity and human and animal health does not lie in the targeted attempt to develop bio-weapons or to specifically re-create pathogens, but in the culture of “just trying something out” coupled with an apparent lack of risk awareness, risk management and safety procedures; this takes place in a culture where the biohazard symbol has become a fashion item.[19]

18 Dziewiaty K. et al (2007): Auswirkungen zunehmender Biomassenutzung (EEG) auf die Artenvielfalt - Erarbeitung von Handlungsempfehlungen für den Schutz der Vögel der Agrarlandschaft. Report for the of environment and nature conservation.

19 The biohazard symbol itself by now has by now become so much part of pop-culture that it is used regularly for bands and as tatoo. See for example http://www.underconsideration.com/speakup/archives/002147.html, http://www.rockabilia.com/band.php?bcat=591&cat=591 and http://www.google.com/search?q=biohazard+tattoo&hl=en&client=ubuntu&sa=G&channel=fs&gl=uk&prmd=imvns&tbm=isch&tbo=u&source=univ&ei=DxSYTr7YHYGgOteizEY&ved=0CDcQsAQ

5.1 Low tech equipment = low safety

A number of projects and articles in the last year hail the work of garage hackers producing Synthetic GMOs with minimal or hacked equipment,[20] the production of equipment like DIY PCR machines for 600$,[21] genetic engineering kits for schools[22] and hacker-spaces for biotechnology.[23]

> "Would-be 'biohackers' around the world are setting up labs in their garages, closets and kitchens - from professional scientists keeping a side project at home to individuals who have never used a pipette before. They buy used lab equipment online, convert webcams into US$10 microscopes and incubate tubes of genetically engineered *Escherichia coli* in their armpits. (It's cheaper than shelling out $100 or more on a 37°C incubator.) [...] For now, most members of the do-it-yourself, or DIY, biology community are hobbyists, rigging up cheap equipment and tackling projects that - although not exactly pushing the boundaries of molecular biology - are creative proof of the hacker principle." (Ledford 2010).

"OpenPCR" had asked for only 6,000 USD to develop a PCR machine that anybody could connect to their laptop.

> "Do you want to explore your own genome, hack together DNA code, build your own biofuel, or prove that the trees in your backyard really are Truffula? You'll need a PCR machine, one of the cornerstones of molecular biology, which costs $4,000 up to $10,000."[24]

Within 10 days this amount was reached and by the end of the funding period the initiators had received more than 12,000 USD. Within less than a year, by July 2011, they were shipping the first machines. Their website now shows support by Nature Biotechnology, Wall Street Journal and GQ.[25] Such a PCR machine can be ordered online and is shipped internationally. The only requirement for the receiver is that they have a screw driver to put it together.

The necessary nucleotides can be bought online for as little as 90 USD plus 25 USD hazmat fee from mail-order companies.[26] Additional tools currently include for example an iPhone app to check the compatibility of chemicals.[27]

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20 See for example Ledford H. (2010): *Life hackers.* Nature 467: 650-652; Riddell A. (2006): Tweaking genes in the basement. Wired, 07.06.06, http://www.wired.com/medtech/health/news/2006/07/71276; or Service R.F. (2011): *A different kind of secret code.* Science, 26 Sept 2011, http://news.sciencemag.org/sciencenow/2011/09/a-different-kind-of-secret-code.html.

21 OpenPCR: http://openpcr.org/ and their crowd-funding project proposal "OpenPCR - open source biotech on your desktop"; http://www.kickstarter.com/projects/930368578/openpcr-open-source-biotech-on-your-desktop

22 "Hello, World!" - Modern Biotechnology for High Schools, crowd-funded at http://www.kickstarter.com/projects/peyer/hello-world-modern-biotechnology-for-high-schools

23 "BioCurious: A Hackerspace for Biotech. The Community Lab for Citizen Science; crowd-funded at http://www.kickstarter.com/projects/1040581998/biocurious-a-hackerspace-for-biotech-the-community

24 OpenPCR project proposal at http://www.kickstarter.com/projects/930368578/openpcr-open-source-biotech-on-your-desktop

25 OpenPCR http://openpcr.org/

26 For example "PCR Nucleotide Mix 200Ul" for 87 USD can be bought from "Disocunt Supply Source": http://www.discountsupplysource.com/Pcr-Nucleotide-Mix-200Ul-p/f-332693.htm

27 http://itunes.apple.com/us/app/chemical-compatibility-database/id408288716?mt=8

While the tools to *make/do* Synthetic Biology and Genetic Engineering in such a set-up are highlighted and funded, there is no mention of affordable safety equipment or waste disposal.

At times, figures for waste disposal of household chemicals, batteries etc show that the general population is unlikely to safely dispose of these items even though there are collection schemes available. It appears unlikely that people who go for DIY equipment to make Synthetic organisms would then spend disproportionately more money on safety equipment or would contact their local waste collector for the closest disposal area for bio-hazard waste.

We therefore have to conclude that in garage biotechnology (Synthetic) GMOs are being developed without appropriate measures to prevent their release into the environment.

5.2 Mail-order DNA

A growing number of companies make DNA sequences to order and ship them world-wide. In 2010, the ETC Group listed about 66 of them, mainly in North America, Europe, Asia, but also in countries like Russia, South Africa and Iran (see above 1.4, p.3)[28] Some of these also integrate the synthetic DNA into vectors on request from customers.[29]

Who is responsible for the risk assessment in these cases? How could somebody be responsible for a risk assessment if they have designed the DNA on a computer and just sent the order to a company and therefore never actually had it in their possession before it was posted to them?

Several examples published in recent years also show how easy it is to order the DNA to recreate pathogens.

> **Ordering Smallpox DNA online**
> "DNA sequences from some of the most deadly pathogens known to man can be bought over the internet, the Guardian has discovered.
> In an investigation which shows the ease with which terrorist organisations could obtain the basic ingredients of biological weapons, this newspaper obtained a short sequence of smallpox DNA. The deadly virus has existed only in laboratories since being eradicated from the world's population 30 years ago.
> The DNA sequence of smallpox, as well as other potentially dangerous pathogens such as poliovirus and 1918 flu are freely available in online public databases. [...]
> The package, which contained a 78-letter sequence of DNA, which is part of one of the smallpox virus's coat protein genes, was delivered by the Royal Mail to a flat in north London. The A5-sized Jiffy bag contained a small plastic phial with a tiny blob of white gel at the bottom - the DNA. The order cost £33.08, plus an additional £7 for postage.

28 ETC Group (2007): *Extreme Genetic Engineering.* Report. Map of Commerical DNA Synthesis Companies, p. 8-9. The companies were located in the USA & Canada, Europe, Russia, India, China, Korea, Taiwan, Japan, Australia, South Africa and Iran.

29 See for example service provided by synthetic gene providor DNA 2.0 marketed as "any sequence in any vector" - https://www.dna20.com/index.php?pageID=303

> Alan Volkers, chairman of VH Bio Ltd said the company had no idea that the sequence they produced was a modified sequence of smallpox DNA."[30]
>
> "New Scientist magazine surveyed 12 gene synthesis companies in North America and Europe. Only five said they always screened their orders for suspect sequences and three said they never did. These were all doing relatively large-scale synthesis, providing sequences a few hundred letters long, but there are many more companies like VH Bio Ltd which make so-called oligonucleotides, sequences around 100 letters or smaller."[31]

It would be close to impossible to ensure that all companies check the sequences customers order from them against a database of known pathogens. First of all it leaves open the question of how much homology between the ordered sequence and a known pathogen would trigger a warning, but secondly there will always be companies willing to send such sequences, just as there are currently companies that are willing to send chemicals and pesticides to countries were they are forbidden by law.[32]

What is mostly highlighted in the public debate, is the possibility to (re)create deadly human diseases, but the risk is just as high for plant and animal diseases. Their release would be a direct threat to biodiversity with all ensuing knock-on effects.

5.3 Treating Synthetic biology as a game!

Garage biotech and articles in the blogging sphere show a lack of knowledge of the safety (precaution) and risk discussions of the last decades.

So far, the argument has at least been about the intention behind transgenic modification, and whether or not its intended use would be likely to cause adverse effects. **Synthetic Biology challenges do not aim for 'benefits' balanced by 'risks' but simply for the most "jaw-dropping" Synthetic GMO**.

At a DARPRA challenge in September 2011, the winning entry was a "a stenographic text-encoding scheme that uses bacteria to encode messages and selective antibiotics to reveal them". Seven colonies of *E.coli* are genetically modified to display different colours, and sets of two of these can be combined to represent letters, numbers and special characters to encode a text. Antibiotic resistance was added, so that it would be possible to add additional colours so that only the right recipient of the text who would treat the 'text' with the right antibiotics would be able to decipher the message. Science hailed this as "the new technique could also allow companies to encode secret identifiers into crops, seeds, or other living commodities."[33] Questions of environmental effects or biosafety with the release of at least seven modified antibiotic resistant *E. coli* strains just to produce coloured dots on nitro-cellulose paper, remain not only unanswered but even unasked.

The use of antibiotic resistance as a selective marker gene has been intensively debated in risk assessment of

30 Randerson J. (2006): *Revealed: the lax laws that could allow assembly of deadly virus DNA.* The Guardian, 14 June 2006.

31 Randerson J. (2006); *Lax laws, virus DNA and potential for terror*. The Guardian, 14 June 2006.

32 See for example Greenpeace (2006): *Krimineller Handel mit verbotenen Pestiziden in Deutschland.* Greenpeace Germany, November 2006.
http://www.greenpeace.de/fileadmin/gpd/user_upload/themen/umweltgifte/greenpeace_handel_illegale_pestizide_01.pdf

33 Service R.F. (2011): *A different kind of secret code.* Science Magazine, 26 Sept. 2011; http://news.sciencemag.org/sciencenow/2011/09/a-different-kind-of-secret-code.html

GMOs.[34] The EU aimed to replace it by other methods. Discussion about its use in GMOs often focuses on the perceived need of antibiotic resistance as 'marker' and/or whether it constituted a risk in a specific case. But in challenges like iGEM or DAPRA they are just another cool item to add.

Treating biotechnology as a game - for example praising somebody for the development of flurescent yoghurt[35] or spreading antibiotic resistant bacteria just because they blink nicely - shows a general lack of understanding of threats to biodiversity.

Turning synthetic biology and genetic engineering into a game overly simplifies the risks associated with GMOs. The following - full - example from iGEM's "Registry of Standard Biological Parts"[36] claims that laboratory strains *E. coli* cannot thrive in the intestine, ignoring the risks of gene exchange between strains, evolutionary adaptation and the threats that *E.coli* can pose.

> **"E. coli can't thrive in the intestine"**
>
> "Escherichia coli is a gram-negative bacterium and a model organism in biological engineering research. Laboratory strains of E. coli, such as E. coli K12, offer attractive chassis for synthetic biology research for several reasons.
>
> - It is one of the most intensively studied model organisms in molecular and cell biology.
> - It has a rapid doubling time of less than an hour, meaning that saturated cultures can be grown overnight.
> - It has lost its ability to thrive in the intestine, so it is a safe, biosafety level 1 organism.
> - There are a wide variety of tools and protocols supporting BioBrick part assembly and propagation as well as protein expression and measurement available.
>
> Most BioBrick parts and devices available in the Registry, unless indicated otherwise, are designed to operate in E. coli."[37]

This is in striking difference to for example information by the WHO that describes *E. coli* as

> "[..] a bacterium that is commonly found in the gut of humans and other warm-blooded animals. While most strains are harmless, some can cause severe food-borne disease. *E. coli* infection is usually transmitted through consumption of contaminated water or food, such as undercooked meat products and raw milk.
> Symptoms of disease include abdominal cramps and diarrhoea, which may be bloody. Fever and vomiting may also occur. Most patients recover within 10 days, although in a few cases the disease may become life-threatening."[38]

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34 See for example the debate over the approval of GM potato Amflora (EH92-527-1) in the EU which especially focussed on the issue of the antibiotic resistance marker nptII. European Medicines Agency (2007): *Presence of the antibiotic resistance marker gene nptII in GM plants for food and feed uses.* EMEA/CVMP/56937/2007- Final. http://www.emea.europa.eu/pdfs/human/opiniongen/5693707en.pdf

35 Ledford (2010)

36 Registry of Standard Biological Parts (2011): *Catalog.* http://partsregistry.org/Catalog; accessed 11 Oct 2011

37 Registry of Standard Biological Parts (2011): *Escherichia coli*. http://partsregistry.org/Escherichia_coli; accessed 11 Oct 2011

38 WHO (2010): *Escherichia coli infections*. http://www.who.int/topics/escherichia_coli_infections/en/index.html

One of the latest example of life-threatening *E.coli* infections was the outbreaks of *E. coli* O104:H4 infection in Germany and 15 other countries in Europe and North-America, killing at least 50 people in Germany alone.[39]

Such blatant over-simplification can lead to real risks to biodiversity when bacteria and yeasts are unknowingly used under the assumption that they are harmless anyway.

iGEM's catalogue of Biological Parts among other items list several thousand items as "Available Protein Coding Regions"[40] among which antibiotic resistance genes are listed indiscriminately just as "markers". The current list includes resistance to kanamycin, chloramphenicol, tetracycline, spectinomycin and hygromycin.[41] Through the "BioBrick Repository" these "DNA Part Repositories" are distributed to iGEM participants on plates of dried DNA.

iGEM teams are judged in their approach to biosafety, by answering the following questions:

Questions to iGEM competition teams

"1. Would any of your project ideas raise safety issues in terms of:

- researcher safety,
- public safety, or
- environmental safety?

2. Do any of the new BioBrick parts (or devices) that you made this year raise any safety issues? If yes,
   - did you document these issues in the Registry?
   - how did you manage to handle the safety issue?
   - How could other teams learn from your experience?
3. Is there a local biosafety group, committee, or review board at your institution?
   - If yes, what does your local biosafety group think about your project?
   - If no, which specific biosafety rules or guidelines do you have to consider in your country?
4. Do you have any other ideas how to deal with safety issues that could be useful for future iGEM competitions? How could parts, devices and systems be made even safer through biosafety engineering?"[42]

Leaving the assessement of Synthetic genetically modified organisms to undergraduates answering three or four questions, is by no means a sufficient risk assessment.

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39 WHO (2010): *International Health Regulations: Outbreaks of E. coli O104:H4 infection.* http://www.euro.who.int/en/what-we-do/health-topics/emergencies/international-health-regulations/outbreaks-of-e.-coli-o104h4-infection

40 http://partsregistry.org/cgi/partsdb/pgroup.cgi?pgroup=Coding

41 http://partsregistry.org/Protein_coding_sequences/Selection_markers

42 http://2011.igem.org/Safety. It is possibly for iGEM teams to answer all questions about whether their new Synthetic GM bacteria pose any risks with "No" as the one of the winning teams of the European competition in October 2011, the Imperial College of London, shows: http://2011.igem.org/Team:Imperial_College_London/Safety and http://2011.igem.org/Team:Imperial_College_London/Human_Containment

5.4 Cartagena Protocol on Biosafety

Both the proliferation of Garage Biotech and existence of international amateur competitions like the annual iGEM jamboree, raise concerns about compliance with the Cartagena Protocol on Biosafety.

It is possible that companies that provide synthetic DNA inserted into bacteria on customers' orders send these to other countries including those that are Parties to the Biosafety Protocol. This would result in a transboundary movement of an LMO (or incorporatable genetic elements) - but as mentioned above, no risk assessment might have been undertaken. This might be under the premises that the organism or the sequences shipped are being perceived as "destined for contained use". But "contained use" is defined differently to garage biotech facilities. Hence advanced informed agreement (AIA) should be obtained. Yet such AIA by the importing country might become close to impossible if the Synthetic bacteria – or even just plasmids - are just sent by post for DIY purposes.

The same question also arises when hundreds of teams of school and university students travel to a 'jamboree'.[43] At the last iGEM meeting at MIT, 130 teams mainly from North America, Europe, Asia participated.[44]

Another example, shows how simple lack of knowledge could result in breaches of the Cartagena Protocol. On the crowd-funding website Indiegogo, somebody from the USA looked for funding to develop a "Radio controlled bacteria" that could be "made to glow with a push of a button".[45] Everybody contributing at least 50 USD to the project would receive "a vial of Glowing Bacteria". Since there are no restrictions on potential funders, this could have resulted in the transboundary movement of a - completely undefined - synthetic LMO.[46]

5.5 Not bio-terrorists, but bio-errors waiting to happen

> "These kit-level experiments are harmless, hobbies pursued as much for educational purposes as for ingenuity. But in the wrong hands, some have warned, more than lives could be threatened."[47]

Quotes like these show the assumption that mistakes or unexpected adverse effects cannot happen: the kits, the access to any sequence of DNA that was ever published, all of this in itself would be harmless and only if somebody with bad intentions get their hands on it, could they become dangerous. Such assumptions are contrary to experience and risk management in a number of fields. Even now diseases and pathogens don't usually spread because somebody has planned this but because of their nature and because of circumstances that make their spread possible.

In the context of Synthetic biology and the CBD, we need to assess the possibilities of the development of not just pathogens but also other organisms that can affect any part of ecosystems (animal, plants, algae, fungi and bacteria) to avoid adverse effects on biodiversity.

43 "Jamboree" is a term typically used for scouts' gatherings.

44 iGEM Jamboree 2010 participants: http://igem.org/Team_List?year=2010

45 kingjacob: Radio Controlled Bacteria. http://www.indiegogo.com/Radio-Controlled-Bacteria

46 The project did not receive sufficient funding in this instance.

47 Farrel J. (2011): *Should Synthetic biology be policed?* Forbes, 23 June 2011. http://blogs.forbes.com/johnfarrell/2011/06/23/should-synthetic-biology-be-policed/

6 Conclusions

Synthetic Biology and the development of Synthetic organisms (Synthetic LMOs /GMOs) need urgent attention from the SBSTTA not only because it is already underway while posing threats to biodiversity that go far beyond genetic engineering, but also because the way how it is done and the places where it is done has moved from research institutions and (agricultural) companies to a much wider range of actors and places. Where so far the creation and assessment of LMOs was in the realm of scientists, Synthetic Biology is actively moved beyond those who have studied the related sciences and understand the risks.

The combination of much more far reaching impacts of Synthetic Biology and many more institutes, companies and people in general doing it, can cause threats far beyond what has previously been addressed to biodiversity worldwide, and it is urgent for the CBD to think and act on it without delay.

7 Resources

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