Secretariat of the Convention on Biological Diversity

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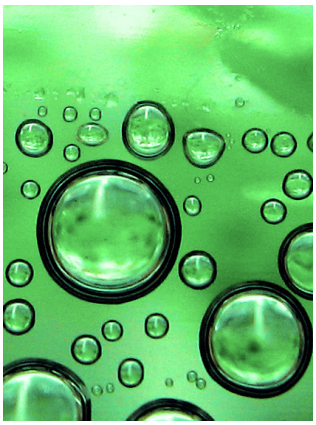

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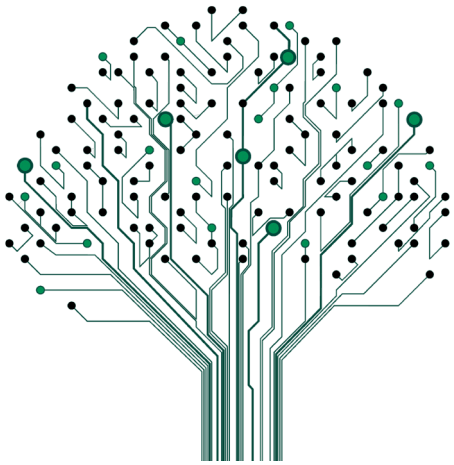
SYNTHETIC BIOLOGY

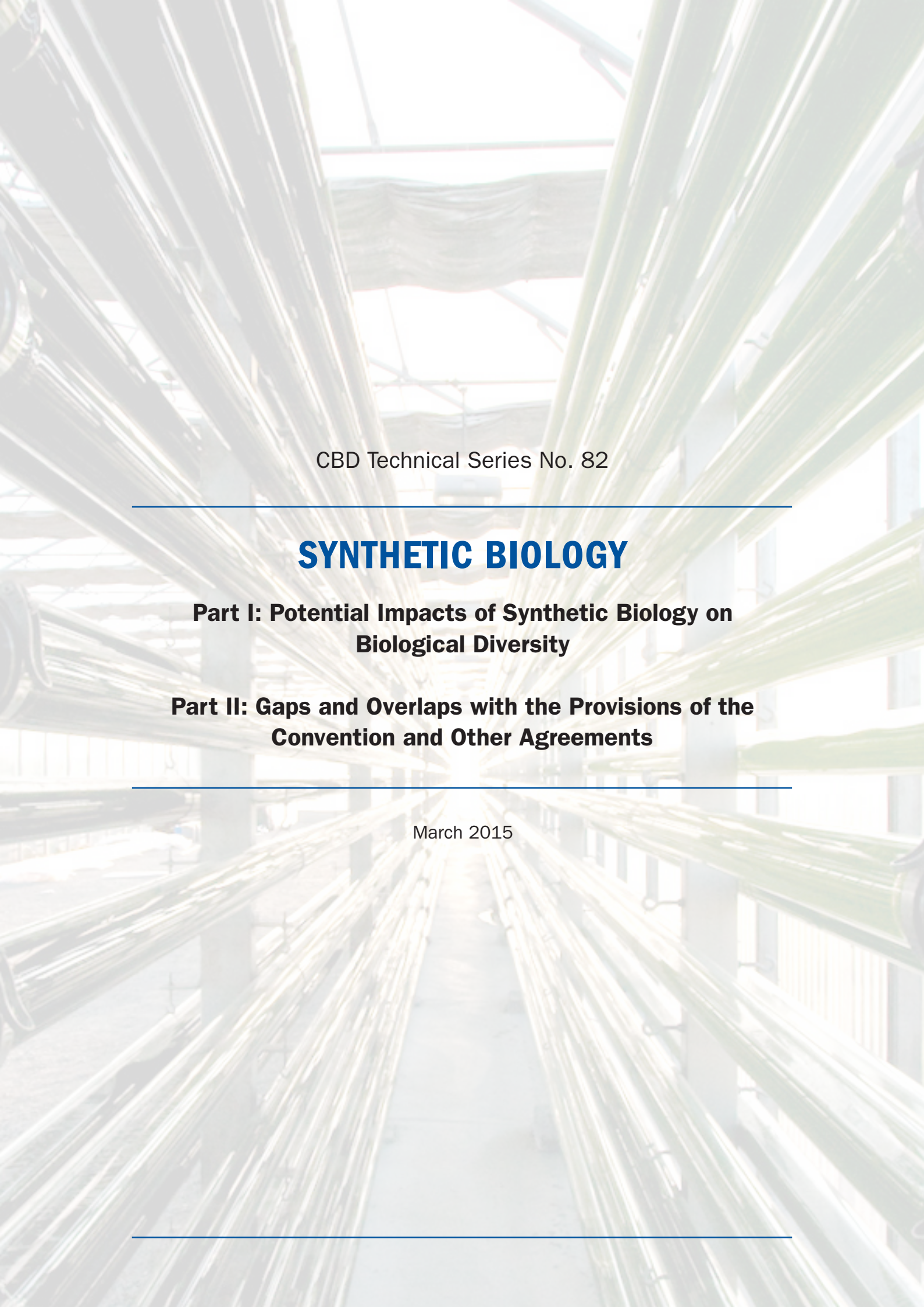


Part I: Potential Impacts of Synthetic Biology on Biological Diversity

Part II: Gaps and Overlaps with the Provisions of the Convention and Other Agreements

UNEP

Convention on Biological Diversity



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SYNTHETIC BIOLOGY

Part I: Potential Impacts of Synthetic Biology on Biological Diversity

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FOREWORD

One of the functions of the Subsidiary Body on Scientific, Technical and Technological Advice to the Convention on Biological Diversity is to identify new and emerging issues relating to the conservation and sustainable use of biodiversity. To streamline the work of the Subsidiary Body, the Conference of the Parties, in decision IX/29, provided guidance on the procedure for the identification of new and emerging issues and on the review of proposals.

The Conference of the Parties first turned its attention to synthetic biology at its tenth meeting in 2010, where Parties, other Governments and relevant organizations were, *inter alia*, invited to apply the precautionary approach to the field release of synthetic life, cell, or genome into the environment. Consideration of synthetic biology as a substantive issue was subsequently placed on the agenda of the Subsidiary Body on Scientific, Technical and Technological Advice at its sixteenth meeting in 2012, and since then it has been debated intensively.

Synthetic biology is a loosely-defined term for a range of techniques stemming from the combination of different disciplines, which adds a challenge to the debate. Moreover, as this field develops quickly, there are many unknowns regarding what products and applications will be technically feasible, commercially viable, and safe both for human health and biodiversity. In addition, questions of the adequacy of existing regulations to deal with current and anticipated components, organisms and products of synthetic biology as well as the social and ethical implications of synthetic biology are being raised.

The current document aims to support the international debate, and bridge gaps between the science-policy interface, by providing technical information on the potential positive and negative impacts on biodiversity that synthetic biology might entail as well as how adequately existing regulations cover the components, organisms and products of synthetic biology. This document was developed on the basis of information and views submitted by Parties to the Convention on Biological Diversity and other stakeholders. It was complemented by background research to address relevant issues under the Convention. An earlier draft of this document was reviewed by the Subsidiary Body on Scientific, Technical and Technological Advice at its eighteenth meeting, and revised in light of the comments provided during that meeting and through a subsequent peer-review process.

It is my hope that this document will help inform the discussions on synthetic biology and that it provides a constructive contribution to the expert process established by the Conference of the Parties in decision XII/24.

Braulio Ferreira de Souza Dias
Executive Secretary,
Convention on Biological Diversity

Source: Christine Cooper

Source: PNNL

BACKGROUND

In decision X/13, the Conference of the Parties invited Parties, other Governments and relevant organizations to submit information on, inter alia, synthetic biology for consideration by the Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA), in accordance with the procedures outlined in decision IX/29, while applying the precautionary approach to the field release of synthetic life, cell or genome into the environment.

Following the consideration of information on synthetic biology by the SBSTTA at its sixteenth meeting, the Conference of the Parties, in decision XI/11, requested the Executive Secretary to, inter alia, invite additional information on the subject, to compile and synthesize this information and to consider possible gaps and overlaps with the applicable provisions of the Convention, its Protocols and other relevant agreements. A synthesis of this information was to be prepared, peer reviewed and subsequently considered by the SBSTTA. The resulting documents, UNEP/CBD/SBSTTA/18/INF/3 and 4, were made available to the eighteenth meeting of the SBSTTA, and, in accordance with the resulting recommendation, subjected to another round of peer review.

On the basis of the comments made at the eighteenth meeting of the SBSTTA and additional comments provided through a peer-review process that took place in July and August 2014, the documents were substantially revised and issued as information documents for consideration by the twelfth meeting of the Conference of the Parties to the Convention on Biological Diversity (UNEP/CBD/COP/12/INF/11 and 12). In decision XII/24, the Conference of the Parties established an Ad Hoc Technical Expert Group (AHTEG) and requested the Executive Secretary to convene a moderated open-ended online forum in support of the work of the AHTEG.

The current document represents the text from the two information documents submitted to the Conference of the Parties, with minor editorial corrections, and is being issued as part of the CBD Technical Series to support the work of the AHTEG. It consists of two parts:

Part I: Potential positive and negative impacts of components, organisms and products resulting from synthetic biology techniques on the conservation and sustainable use of biodiversity, and associated social, economic and cultural considerations; and

Part II: Possible gaps and overlaps with the applicable provisions of the convention, its protocols and other relevant agreements related to components, organisms and products resulting from synthetic biology techniques.

ACKNOWLEDGEMENTS

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Source: PNNL

PART I

POTENTIAL POSITIVE AND NEGATIVE IMPACTS OF COMPONENTS, ORGANISMS AND PRODUCTS RESULTING FROM SYNTHETIC BIOLOGY TECHNIQUES ON THE CONSERVATION AND SUSTAINABLE USE OF BIODIVERSITY, AND ASSOCIATED SOCIAL, ECONOMIC AND CULTURAL CONSIDERATIONS

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CONTENTS

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A. EXECUTIVE SUMMARY

Synthetic biology falls within the scope of biotechnology, as defined by the Convention on Biological Diversity i.e. "... any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use." Synthetic biology methodologies and techniques share various degrees of overlap with those of "modern biotechnology" and, in particular, the "application of *in vitro* nucleic acid techniques [...] that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection" as defined in the Cartagena Protocol on Biosafety.

While there is no internationally agreed definition of "synthetic biology", key features of synthetic biology include the "*de novo*" synthesis of genetic material and an engineering-based approach to develop components, organisms and products. Synthetic biology builds on modern biotechnology methodologies and techniques such as high throughput DNA technologies and bioinformatics. There is general agreement that the processes of synthetic biology aim to exercise control in the design, characterization and construction of biological parts, devices and systems to create more predictable biological systems. The areas of research that are considered "synthetic biology" include DNA-based circuits, synthetic metabolic pathway engineering, synthetic genomics, protocell construction, and xenobiology:

- **DNA-based circuits** involve the rational design of sequences of DNA to create biological circuits with predictable, discrete functions, which can then be combined in modular fashion in various cell hosts. Genetic circuits are seen to function in a manner analogous to electronic logic components, like switches and oscillators;
- **Synthetic metabolic pathway engineering** aims to redesign or rebuild metabolic pathways, to synthesize a specific molecule from the "cell factory." A synthetic pathway (typically based on naturally occurring DNA sequences that are computer 'optimized') is added to the cell, and then classic genetic engineering tools may be used to increase the desired output;
- **Synthetic genomics** focuses on the genome as the "causal engine" of the cell. Top-down synthetic genomics starts with a whole genome, from which researchers gradually remove "non-essential" genes to pare down to the smallest possible genome size at which the cell can function as desired. The primary goal is to craft a simplified "chassis" to which modular DNA "parts" can be added. Bottom-up synthetic genomics aims to build functional genomes from pieces of synthesized DNA. At this point, natural genomes are needed as models because of the many DNA sequences that are necessary but have unknown functions;
- **Protocell construction** aims to create the simplest possible components to sustain reproduction, self-maintenance, metabolism and evolution. Thus this research seeks to design for less complexity at the cellular level (rather than at the genome level as in the case of genome-level engineering);
- **Xenobiology** (also known as chemical synthetic biology) is the study and development of life forms based on biochemistry not found in nature. Xenobiology aims to alter DNA and RNA to produce XNA (xeno-nucleic acids) and novel proteins. Xenobiology is often cited as a potential "built-in" biocontainment mechanism to prevent gene transfer to wild organisms.

Current and near-term commercial and industrial applications of synthetic biology aim at creating micro-organisms that synthesise products for fuels, pharmaceuticals, chemicals, flavorings and fragrances. The majority of these applications of synthetic biology engineer microbes, such as the frequently-used *E. coli*, baker's yeast (*Saccharomyces cerevisiae*) and microalgae, to produce alternatives to naturally-occurring or petroleum-based molecules. One such example is the production of artemisinic acid in engineered yeast with the aim of manufacturing an alternative to the naturally occurring anti-malarial drug artemisinin,

which is derived from *Artemisia* plants. Another example is the production of fuels such as biodiesel and isobutanol using synthetic biology techniques. Synthetic biology techniques are also being explored and used for the production of pharmaceutical drugs (e.g. to lower blood sugar levels in adults with type 2 diabetes) and flavourings/fragrances (e.g. vanillin). Although many of the anticipated results of synthetic biology are highly speculative, synthetic biology, in combination with modern biotechnology techniques, is producing current and near-term commercial products and industrial processes. The global synthetic biology market was estimated to be $1.1 billion in 2010, and predicted to be $10.8 billion by 2016. This market includes products for practicing synthetic biology techniques, such as commercially-available stretches of synthesized DNA and the BioBrick™ Assembly Kit, as well as products produced using synthetic biology techniques.

Components, organisms and products of synthetic biology may have some positive impacts on the conservation and sustainable use of biodiversity. Many of the applications of synthetic biology aim at developing more efficient and effective ways to respond to challenges associated with bioenergy, environment, wildlife, agriculture, health and chemical production. Potentially, positive impacts may be realized in a number of ways, including, for example:

- The development of micro-organisms designed for bioremediation and biosensors resulting in pollution control and remediation of environmental media;
- Synthesizing products such as chemicals or drug precursors that are currently extracted from plant or animal sources, thereby reducing the pressure on wild species that are currently threatened due to over harvesting or hunting;
- Developing organisms designed to generate biofuels which may lead to decreased dependence on non-renewable energy sources;
- In building on the achievements of modern biotechnology in producing agricultural crops that are tolerant to abiotic stress and pests, synthetic biology techniques that are more bioinformatics and computer assisted may potentially have the capability to further refine expression and environmental persistence of the products in the organism;
- Restoring genetic diversity through reintroducing extinct alleles, or even "de-extinction" of species.

Organisms and products of synthetic biology could also have some negative impacts on the conservation and sustainable use of biodiversity including, for example:

- Microbes that are intended for release into the environment could have adverse effects due to their potential for survival, persistence and transfer of genetic material to other micro-organisms;
- Potential undesired consequences could result from the use of "gene drive" systems to spread traits aimed at the suppression or extirpation of populations of disease vectors (e.g. mosquitoes). One such undesired consequence could be the introduction of new diseases through the replacement of the population of the original disease vector by another vector species ("niche substitution");
- Possible toxic and other negative effects on non-target organisms such as soil micro-organisms, beneficial insects, other animals and plants;
- Potential negative impacts to the conservation and sustainable use of biodiversity could arise from the transfer of genetic material to wild populations via vertical gene transfer and introgression.

Synthetic biology applications could also have indirect negative impacts on the conservation and sustainable use of biodiversity arising from a large-scale increase in the utilization of biomass. Much of the synthetic biology research is focused on designing organisms that will use biomass as feedstock to produce fuels, chemicals, and pharmaceuticals. Some applications, e.g. fuel production, would require high amounts of biomass, which could lead to a rapid decline in soil fertility and structure, and contribute to biodiversity loss and climate change through direct and indirect land-use change.

The level of exposure of the environment to organisms and products of synthetic biology will determine the level of biosafety-related concerns. In order to mitigate some of the potential negative impacts on the conservation and sustainable use of biodiversity posed by organisms developed through synthetic biology, containment strategies can be used during their handling. Most of the current and near-term applications of synthetic biology involve living organisms that are intended for contained use in research laboratories and industrial settings. Limited biosafety concerns have been raised for organisms

Source: Macroscopic Solutions, LLC

being kept under strict containment conditions and focus on ensuring that appropriate measures are in place to prevent contact with the external environment through unintentional or unauthorized releases. Where applicable, organisms produced through synthetic biology may also be placed under contained use outside of laboratories and industrial facilities by using physical measures to limit their exposure to the environment. However, there is no consensus regarding the degree of physical containment that is needed for organisms developed through synthetic biology. Another emerging strategy is the use of synthetic biology techniques to develop organisms that have integrated biocontainment traits as in-built biosafety measures. This can include, for example, the use of trophic containment, introduction of suicide genes or xenobiology, i.e. the use of nucleic acids that contain components that are not found in nature and, therefore, should not hybridize with naturally occurring organisms. There is, however, debate on the efficacy of any biocontainment strategy and whether such systems will ever be fully functional or fail proof.

Applications where the organisms that have been produced using synthetic biology techniques and are intended for environmental release will likely raise different biosafety concerns than those of organisms intended for contained use. Organisms produced through synthetic biology and introduced into the environment may have adverse effects on the conservation and sustainable use of biodiversity. This includes the potential for invasiveness of the organism which may lead to an adverse effect on native species through the destruction of habitat or a disruption of the trophic cascade. Genes from organisms developed through synthetic biology techniques could also transfer to unrelated species through horizontal or vertical gene transfer which may lead to a loss of genetic diversity and an unintended spread of phenotypic traits. Other unintentional adverse effects may occur and must be assessed on a case-by-case basis. Current provisions and procedures established under the Cartagena Protocol on Biosafety, at the international level, and in many existing national biosafety legislations, at the national level, can effectively cover these areas of biosafety concerns.

Existing biosafety risk assessment frameworks are likely to be sufficient to assess the risks of current and near-term applications of synthetic biology on the conservation and sustainable use of biodiversity. As synthetic biology develops, this assessment may need to be revisited. Most existing biosafety regulations, including the Cartagena Protocol on Biosafety, rely on case-by-case assessments of risks which take into account the environment which will be exposed to the organism, the characteristics of the organism and its intended uses. Current and near-term commercial applications of synthetic biology build on techniques of modern biotechnology to create organisms with novel combinations of genetic material. As such, the general risk assessment methodology for living modified organisms is expected to be applicable to organisms produced through synthetic biology, albeit specific consideration will likely be needed to identify any gaps that exist in the risk assessment methodologies that are currently in place for living modified organisms and propose guidance on how to fill such gaps. If and when future commercial applications of synthetic biology evolve to use techniques that do not rely on the in vitro manipulation of nucleic acids to cause inheritable changes in an organism, current risk assessment methodologies for living modified organisms may no longer be suitable. Some researchers reflect concern for the "unknown unknowns" of synthetic biology in their call for significantly increased funding for dedicated synthetic biology risk research. They argue that no one yet understands the risks that synthetic organisms pose to the environment, what kinds of information are needed to support rigorous assessments, or who should collect such data.

Synthetic biology could cause major economic shifts with positive and negative consequences. If research in synthetic biology develops as many anticipate – or if current commercial and industrial applications of synthetic biology expand in scale – synthetic biology could cause an economic paradigm shift towards economies in which biotechnology, or industries based on the use of biological resources, contribute a much more significant share. However, how developing countries would fare in such a global "bioeconomy" is not self-evident. As seen with other technologies, it is possible that synthetic biology applications would contribute to economic growth if adopted as niche technologies by developing economies. Moreover, synthetic biology could benefit the economies of developing countries through specific applications where the tropics and sub-tropics could be major sources of the biomass needed as feedstock for bio-based processes. It is also possible that a biotechnology-led bioeconomy would reinforce inequitable trends in international trade; that the scale of extraction and use of biomass to provide for a global bioeconomy could be ecologically unsustainable; and that natural products currently grown or harvested would be displaced by industrial production from micro-organisms resulting from synthetic biology techniques. The shape of new bioeconomies and their social, economic and cultural impacts will likely be influenced by government policies and regulations.

From a health and social perspective, synthetic biology may bring benefits but also unintended effects. In relation to human health, further developments in synthetic

biology could lead to positive impacts by helping to understand disease mechanisms and through the discovery of new drugs, development of vaccines, gene therapies and diagnostic tools. As is historically the case in human health research, unintentional negative effects from drugs and therapies resulting from synthetic biology techniques may trigger unanticipated adverse effects on human health. Synthetic biology techniques may provide tools to better detect and identify pathogenic agents and responding to biosecurity threats. On the other hand, the components, organisms or products of synthetic biology used in research may also be used for damaging results, such as creating biological weapons or pathogens that target natural resources. In addition to the potential negative environmental impacts mentioned in paragraphs 5 and 6 above, there is also concern around the social impacts of increased biomass use for the production of fuels, chemicals and pharmaceuticals by organisms engineered through synthetic biology. For example, an increase in the demand for biomass could cause communities to lose access to local natural resources and small-scale subsistence farming to be replaced by large-scale commercial farming practices.

Like other modern biotechnologies, synthetic biology raises ethical questions around the level of predictability of its positive and negative impacts, and how to weigh anticipated impacts and the possibility of unexpected impacts. Ethicists debate whether the threshold between the modification of existing organisms and the creation of *de novo* organisms has been crossed, and what the ethical implications of this might be. There are also concerns surrounding the effect of synthetic biology on the public perception of biodiversity and conservation. For example, one of the specific applications of synthetic biology are "de-extinction" projects which raise ethical issues, such as how best to weigh and balance a project's potential harms and benefits, how limited resources for conservation should be directed, and whether support for *in situ* conservation might be seen as less pressing due to the expectation that 'lost' species can be resurrected.

Intellectual property right regimes are still developing around synthetic biology, and could impact the development of the field and specific applications. Two main models of intellectual property for synthetic biology techniques, components, organisms and products seem to be forming: a system with heavy reliance on patenting the components, organisms and products of synthetic biology, and a system based on a combination of patenting the end organisms and products of synthetic biology while sharing the use of the components (e.g. DNA sequences, methods, software) used in the development of such organisms and products. Depending on the intellectual property rights regime that is mostly applied, innovation in synthetic biology may be encouraged, stifled, or directed towards certain kinds of applications or users.

Source: Michael McCullough

Source: EMSL

B. PREAMBLE

Synthetic biology falls within the scope of biotechnology, as defined by the Convention on Biological Diversity i.e. "... any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use." Synthetic biology methodologies and techniques share various degrees of overlap with those of "modern biotechnology" and, in particular, the "application of *in vitro* nucleic acid techniques [...] that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection" as defined in the Cartagena Protocol on Biosafety.

During the peer-review process of this document, many reviewers noted that current and near-term[1] commercial applications of synthetic biology build on techniques of modern biotechnology to create organisms with novel combinations of genetic material. As a result, many of the examples of organisms developed through synthetic biology which are given throughout the document are also "living modified organisms" (LMOs) as defined in the Cartagena Protocol on Biosafety as "...any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology".

The term "classic genetic engineering" is used in this document, where necessary, to distinguish organisms resulting uniquely from modern biotechnology techniques from those organisms resulting from synthetic biology techniques combined with modern biotechnology.

1 *For the purposes of this document, "near-term" applications are those expected to be fully developed during the next 5 to 10 years.*

Source: PNNL

Source: PNNL

C. TECHNICAL BACKGROUND ON SYNTHETIC BIOLOGY

1. INTRODUCTION

While there is no internationally agreed definition of "synthetic biology", key features of synthetic biology include the "de novo" synthesis of genetic material and an engineering-based approach to develop components, organisms and products. Synthetic biology builds on modern biotechnology methodologies and techniques such as high throughput DNA technologies and bioinformatics.

One of the most commonly cited definitions of synthetic biology is: (i) the design and construction of new biological parts, devices, and systems, and (ii) the re-design of existing, natural biological systems for useful purposes.[2] Furthermore, following a request by the European Commission, a consultative process among three Scientific Committees arrived at an operational definition whereby synthetic biology "is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms to alter living or non-living materials" (European Commission 2014).

Synthetic biology represents a shift in the driving forces of biology, from discovery and observation to hypothesis and synthesis (Benner and Sismour 2005; Kitney and Freemont 2012; Lim *et al*. 2012; Sole *et al*. 2007). Synthetic biology tools provide opportunities for the "empirical validation of model-driven hypotheses" (Esvelt and Wang 2013). Weber and Fussenegger (2012) refer to it as "analysis by synthesis". While research in synthetic biology may lead to findings on the "origin of life" and a greater understanding of the essential functions of genomes, the majority of research is focused on commercial and industrial applications (EGE 2009; Lam *et al*. 2009; O'Malley *et al*. 2007; IRGC 2010).

The term "synthetic" has been used by geneticists and biologists decades before the term "synthetic biology" was coined, e.g. "synthetic lethality" (Lucchesi 1967) and "synthetic phenotype" (Guarente 1993). In fact, the synthesis of DNA molecules dates over 30 years ago (Gait 1984). The current use of the term "synthetic biology" arose in the early 2000s to distinguish this emerging area of science from classic genetic engineering (O'Malley *et al*. 2007; Campos 2009). In 2004, the Massachusetts Institute of Technology (MIT, USA) hosted "the First International Meeting on Synthetic Biology," SB1.0.[3] In 2007 the number of annual academic publications on synthetic biology first *exceeded* 100 (Oldham *et al*. 2012). The global synthetic biology market reached nearly $2.1 billion in 2012 and $2.7 billion in 2013. This market is expected to grow to $11.8 billion in 2018 with a compound annual growth rate of 34.4% over the five-year period from 2013 to 2018.[4] Forty countries are in the "core landscape of research" on synthetic biology; most research happens in the USA and European countries, but other sites of major research include China, Brazil, India, Mexico, Argentina, South Africa and Singapore (Oldham *et al*. 2012). Oldham *et al*. (2012) found 530 funding sources for published synthetic biology research, the majority from government agencies and national coalitions such as the US National Science Foundation, the European Union

2 *This definition is found at www.syntheticbiology.org, hosted on OpenWetWare. The site was started by individuals at MIT and Harvard and can be edited by "all members of the Synthetic Biology community." Accessed on 6 May 2013.*

3 *In July 2013, SB6.0, the "Sixth International Meeting on Synthetic Biology" was held in London, UK.*

4 *See Synthetic Biology: Global Markets, at http://www.bccresearch.com/market-research/biotechnology/synthetic-biology-bio066c.html, accessed on 17 September 2014.*

Source: PNNL

Framework programme, and the Human Frontier Science Foundation.[5] A 2013 mapping of synthetic biology research and commercial production by the Woodrow Wilson International Center for Scholars (WWICS 2013a) found a total of 508 unique entities conducting synthetic biology research, which includes 192 companies and 204 universities. The top five application focuses of designers/manufacturers conducting synthetic biology research were medicine; specialty/fine chemicals; fuels and fuel additives; plastics, polymers and rubbers; and plant feedstocks for microbe consumption (WWICS 2013a).

Disagreement over a definition for synthetic biology is tied to differing views on the novelty of the field of synthetic biology and its relationship with classic genetic engineering (Nielsen & Keasling 2011; PCSBI 2010; Zhang *et al*. 2011). Synthetic biology applications use many techniques that are primarily extensions of classic genetic engineering aided by greater computing power. As such, there are two ways in which synthetic biology is often distinguished from classic genetic engineering: (i) in terms of the methods that are adopted, and (ii) in terms of the sophistication and complexity of the work (Tait 2009). Even within scientific communities, there are differences of opinion on whether synthetic biology is revolutionary or an incremental advancement of biotechnology (PCSBI 2010; Zhang *et al*. 2011). This range of viewpoints leads to different perspectives, both on the status of current synthetic biology applications and on expectations for the future of synthetic biology. The majority of current and near-term commercial and industrial applications of synthetic biology use synthetic DNA-circuits and metabolic pathway engineering. These two approaches are rooted in techniques of classic genetic engineering and, depending on one's perspective, may not be considered synthetic biology. Thus, synthetic biology deals almost entirely with theoretical applications and is currently mostly restricted to research laboratories.[6] From a broader view, commercial, industrial, and research applications of synthetic biology are already happening and are rapidly proliferating (Industrial Biotechnology 2014). Expectations for the future of synthetic biology also differ. If synthetic biology lives up to its perceived potential, predictable and rational design of biological components and systems could usher in a new paradigm for biology. But it is unclear if or when this will happen. Many of the future synthetic biology applications aim at positively impacting biodiversity and would require environmental release, thus posing different biosafety concerns as compared to the current uses under containment (Anderson *et al*. 2012).

5 *The Human Frontier Science Program is an international programme established by Australia, Canada, France, Germany, India, Italy, Japan, South Korea, Norway, New Zealand, Switzerland, the UK, the European Union and the United States (Oldham et al. 2012, 10).*

6 *As reported by CBD Parties in their submissions on new and emerging issues that synthetic biology is at the phase of concept testing in laboratories.*

Source: PNNL

Source: Macroscopic Solutions, LLC

Box 1.	Definition of Synthetic Biology
Richard Kitney and Paul Freemont (synthetic biologists)	There is, in some quarters, still doubt about the definition of synthetic biology. This is not a view held by the international synthetic biology community....The accepted definition is "synthetic biology aims to design and engineer biologically based parts, novel devices and systems – as well as redesigning existing, natural biological systems." (Kitney and Freemont 2012)
US Presidential Commission for the Study of Bioethical Issues	Synthetic biology is the name given to an emerging field of research that combines elements of biology, engineering, genetics, chemistry, and computer science. The diverse but related endeavors that fall under its umbrella rely on chemically synthesized DNA, along with standardized and automatable processes, to create new biochemical systems or organisms with novel or enhanced characteristics. (PCSBI 2010)
International Civil Society Working Group on Synthetic Biology	Synthetic biology broadly refers to the use of computer-assisted, biological engineering to design and construct new synthetic biological parts, devices and systems that do not exist in nature and the redesign of existing biological organisms, particularly from modular parts. Synthetic biology attempts to bring a predictive engineering approach to genetic engineering using genetic 'parts' that are thought to be well characterized and whose behavior can be rationally predicted. (ICSWGSB 2011)
Carolyn M.C. Lam, Miguel Godinho, and Vítor A.P. Martins dos Santos (synthetic biologists	Synthetic biology is a field that aims to create artificial cellular or non-cellular biological components with functions that cannot be found in the natural environment as well as systems made of well-defined parts that resemble living cells and known biological properties via a different architecture. (Lam *et al*. 2009)
Scientific Committees to the European Commission	SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms to alter living or non-living materials (European Commission 2014).*
UK Royal Academy of Engineering	Synthetic biology aims to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems (RAE 2009).
Thomas Murray (bioethicist)	"Synthetic biology embodies: a faith that biological systems can be brought to heel, and made predictable and controllable; a stance toward the intricacy of biological organisms aptly described by Tom Knight as an "alternative to understanding complexity is to get rid of it"; a confidence that biological entities can be hacked apart and reassembled to satisfy human curiosity and to serve important, legitimate human purposes; a *hope* that error and malevolence can be deterred, contained or out manoeuvred through the vigilance of governments and, especially, the collective efforts of well-intentioned scientists, engineers and garage biologists" (Various 2009).

* The first preliminary opinion on "Synthetic Biology – Definition" comprises a survey of more than 30 definitions (European Commission 2014).

2. SUPPORTING TECHNOLOGIES

Synthetic biology relies on a suite of supporting technologies, which are also used in classic genetic engineering, that have become dramatically faster and less expensive since the 1990s (RAE 2009; Garfinkel and Friedman 2010). Computational modeling and the connected fields of bio-informatics and information sciences have catalyzed synthetic biology research by making simulation possible and *in silico* testing of biological systems (Schmidt 2009; Esvelt and Wang 2013). The ability to sequence DNA – to determine the order of nucleotides within a molecule of DNA – is key to all areas of synthetic biology research. Scientists have been able to sequence and analyze DNA since the 1970s, but high-throughput next generation sequencing methods and computer programmes make it possible to read longer lengths of DNA at much faster speeds for less money, often by aligning short sequences of overlapping stretches of DNA through computer analysis. Using metagenomic tools, scientists are able to sequence many microbial organisms in an environment at once and thus identify novel, potentially useful, systems (RAE 2009). The term "omics" is sometimes used to group the profiling techniques that analyze biological systems at the genomic, transcriptomic, proteomic and metaboliclevels (Joyce and Palsson 2006).

The ability to chemically synthesize DNA also dates to the early 1970s (Garfinkel *et al*. 2007). The introduction of automated DNA synthesis machines has saved time and effort on the part of researchers using synthesized DNA for experiments (Garfinkel and Friedman 2010; Schmidt 2009). Oligonucleotides, short strands of DNA between 25 to 100 nucleotides in length, can still be produced in individual laboratories, but it is becoming far more common for laboratories to simply order them from commercial companies (Garfinkel *et al*. 2007). Using proprietary techniques, machines can also create DNA strands up to the size of a gene, hundreds or thousands of base pairs in length. Techniques for DNA assembly have also advanced, with laboratories having developed various *in vivo* assembly systems by which genome-length DNA strands can be assembled at once within a cell (Baker 2011). For example, the "Gibson assembly" isothermal method uses a reagent-enzyme mix to assemble multiple fragments of DNA in a single reaction (Gibson *et al*. 2009). DNA synthesis technologies are not yet "mature enough for the convenient and economical engineering of large genomes" (Ma *et al*. 2012). Nonetheless, it is widely anticipated that tools for DNA synthesis will continue to dramatically drop in price and expand the size and reliability of production (POST 2008; Carlson 2009; Schmidt 2010). J. Craig Venter has described the movement of biological information into and out of computers as "biological teleportation": sequencing on-site genomes, placing and retrieving sequence information on the internet, and converting them back into DNA sequences (Industrial Biotechnology 2014).

Directed evolution is a supporting biotechnology method often employed for synthetic biology (Cobb *et al*. 2012; Erickson *et al*. 2011). Researchers create a range of variations in a biological entity and apply selective pressure to them with the goal of identifying those with desired properties. This can be done physically in the laboratory or on a computer (*in silico*), using bioinformatic tools to predict the fitness of sequences (Cobb *et al*. 2012). Various tools can be used to create the variations. For example, through gene knockout, single or multiple genes are either disabled or removed from a genome (Burgard *et al*. 2003). Another technique is gene shuffling, in which DNA is randomly fragmented and reassembled, and the results are tested for such properties as increased enzyme activity and improved functions of specific proteins (Skerker *et al*. 2009). Furthermore, genome shuffling can be used to rapidly evolve the genomes of microbes. For example, Harvard's Wyss Institute has developed a technology called multiplex automated genome engineering (MAGE).[7] They used MAGE to optimize a pathway in *Escherichia coli*, simultaneously modifying 24 genetic components, producing over 4.3 billion combinatorial genomic variants per day, which were then screened for desirable traits (Wang *et al*. 2009). Such techniques can be applied to microbes already transformed with or built from synthetic DNA, as a way to further fine tune for specific results, and can also be used for de novo protein synthesis (Reetz and Carballeira 2007; Hidalgo *et al*. 2008; Dougherty and Arnold 2009).

Synthetic biology also employs techniques for genome editing using sequence-specific nucleases, such as zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALEN), and clustered regularly interspaced short palindromic repeats (CRISPR) which can be engineered to bind to DNA sequences in specific manners (Carroll 2013; Lienert 2014). TALENs were used, for example, to create a mutation in rice aiming at increasing its

7 *See http://wyss.harvard.edu/viewpage/330/, accessed on 23 March 2013.*

resistance to the bacterial pathogen *Xanthomonas oryzae*, which causes a blight disease responsible for significant losses in rice productivity (Li *et al*. 2012). Other synthetic biology approaches rely on techniques for epigenetic modifications, such as RNA-directed DNA Methylation (RDDM), which was first described by Wassenegger *et al*. (1994). Epigenetic modifications are caused by chemical additions to DNA and histones that are associated with changes in gene expression and are heritable but do not alter the primary DNA sequence (Law and Jacobsen 2010).

3. AREAS OF SYNTHETIC BIOLOGY RESEARCH

There is general agreement that the processes of synthetic biology aim to exercise control in the design, characterization and construction of biological parts, devices and systems to create more predictable biological systems (Nuffield 2012; ICSWGSB 2011; Kitney and Freemont 2012; PCSBI 2010; ECNH 2010). Sometimes described as a "converging technology," synthetic biology brings together and builds upon multiple fields, including engineering, molecular biology, information technology, nanobiotechnology, and systems biology (also known as systeomics) (EGE 2009; PCSBI 2010; RAE 2009). Synthetic biology uses available technologies for genetic modification, but in particular aims at the acceleration and facilitation of the process; this includes increasing its predictability (European Community 2014).

The areas of research that are considered "synthetic biology"[8] include DNA-based circuits, synthetic metabolic pathway engineering, synthetic genomics, protocell construction, and xenobiology.

3.1 DNA-based circuits

The goal of this area of synthetic biology research is the rational design of sequences of DNA to create biological circuits with predictable, discrete functions, which can then be combined in modular fashion in various cell hosts. Genetic circuits are seen to function as electronic logic components, like switches and oscillators (Lam *et al* 2009; Heinemann and Panke 2006). The idea of interchangeable, discrete parts that can be combined in modular fashion is "one of the underlying promises of the whole approach of synthetic biology" (Garfinkel and Friedman 2010). Initial circuits were conceptually simple, such as the "Toggle Switch" (Gardner *et al*. 2000) and the "repressilator" (Elowitz & Liebler 2000); these have been combined and built upon to create more sophisticated "devices", such as biosensors (Marchisio & Rudolf 2011). The cells used in this research are often prokaryotic, but research is also occurring in eukaryotic cells such as yeasts and mammalian cells (Lienert *et al*. 2014; Marchisio & Rudolf 2011; Wieland & Fussenegger 2012). DNA-based circuits and synthetic metabolic pathway engineering (see section 3.2) are sometimes considered together because DNA-based circuits are often deployed in engineering metabolic pathway changes (Pauwels *et al*. 2012).

This is the area of synthetic biology that most directly aims to "make biology into an engineering discipline" (O'Malley *et al*. 2007). Bioengineer Drew Endy's foundational 2005 paper in Nature, applied three ideas from engineering to biology: standardization of basic biological parts and conditions to support their use; the decoupling of design from fabrication; and using hierarchies of abstraction so that one could work at a specific level of complexity without regard to other levels. One of the earliest and highest profile standardization systems for the design of DNA "parts" was established by scientists and engineers at MIT in 2003. BioBricks™, sequences of DNA encoding a biological function, are intended to be modular parts that can be mixed and matched by researchers designing their own devices and systems. A major platform for demonstrated uses of BioBricks™ has been the annual International Genetically Engineered Machine competition (iGEM).[9] The iGEM Foundation (which runs the competition) also hosts an open website, the Registry of Standard Biological Parts,[10] where researchers share the DNA sequences for parts designed following BioBrick™ standards. Since 2004, iGEM has provided a platform for undergraduate students to build biological systems using existing BioBricks™ and designing original parts.[11] It has grown rapidly, launching a high school division in 2011 and an Entrepreneurial Division in 2012. The 2012 iGEM competition had 190 teams, with over

8 *Other areas of research sometimes included within synthetic biology include engineered synthetic multicellularity and the design of microbia consortia that communicate across species and coordinate towards human-specified ends (Lam et al. 2009; Maharbiz 2012). These areas are not discussed in this document because they are not frequently included when synthetic biology is discussed, and commentators have not addressed them in terms of their implications for ethics, biosafety, biosecurity, or other aspects.*

9 *See http://igem.org/About, accessed 22 Feb. 2013.*

10 *See http://parts.igem.org/Main_Page, accessed 15 August 2014.*

11 *As discussed in section 7.3 on social aspects of containment, the iGEM competition also requires that participants reflect upon potential impacts of their projects.*

3000 participants from 34 countries. Thanks to the Registry of Standard Biological Parts and iGEM, and perhaps also its appealing and accessible analogy with Lego® pieces, this is one of the most publicly prominent areas of synthetic biology research, experimentation and development (O'Malley *et al*. 2007; Collins 2012; ECNH 2010; PCSBI 2010). Although the Registry of Standard Biological Parts is a non-profit organization, there are also commercial entities using proprietary systems to produce libraries of modular parts. For example, Intrexon, a privately held biotechnology company, advertises its UltraVector® platform as "an operating system comprising advanced DNA construction technologies, cellular and protein engineering, computational models and statistical methods which facilitate the rapid design, testing and production of complex biological systems".[12]

The current reality of DNA circuit construction is far from the simplified modularity of engineering; but modularity continues to be promised on the horizon. In 2006, Heinemann & Panke (2006) noted that the design process for genetic networks was still an iterative process, containing "considerable elements of trial and error". In 2012, this was still the case, as Schmidt and de Lorenzo (2012) explained that the ability to forward-engineer devices with more than 20 genes or parts was limited by a lack of understanding of genes, still requiring reliance on trial and error. Additionally, the Registry of Standard Biological Parts includes thousands of parts, but many are undefined, incompletely characterized, and/or do not work as described (Kwok 2010; Baker 2011).[13] In 2009, the International Open Facility Advancing Biotechnology (BIOFAB) was formed, initially with a grant from the US National Science Foundation, to address these problems. BIOFAB has been working to create a library of professionally developed and characterized parts in the public domain (Baker 2011; Mutalik *et al*. 2013a, b).[14] In 2013, BIOFAB announced that its researchers had established mathematical models to predict and characterize "thousands of high quality standard biological parts".[15]

3.2. Synthetic metabolic pathway engineering

This is an area of research that aims to redesign or rebuild metabolic pathways in order to synthesize a specific molecule from a "cell factory" (Lam *et al*. 2009; Nielsen and Keasling 2011). There is disagreement over whether metabolic pathway engineering may indeed be considered an approach of synthetic biology or as classic genetic engineering, which was rebranded as synthetic biology to take advantage of the hype over synthetic biology (Porcar and Pereto 2012; Various 2009). In support of the former, Nielsen and Keasling (2011) explain that while in metabolic engineering done through classic genetic engineering, an organism that naturally produces the desired chemical is improved through strain breeding or genetic modification to increase production, synthetic biology enables scientists to start with a "platform cell factory" that would not naturally produce *any* of the chemical. A synthetic pathway (rationally designed or based on a natural sequence but computer optimized) is added to the cell, and then classic genetic engineering tools may be used to increase the desired output (Nielsen and Keasling 2011; Venter 2010). Some also claim that the aim of synthetic biology to systematically engineer metabolic interactions sets it apart from metabolic engineering done through classic genetic engineering (Arkin and Fletcher 2006; Lam *et al*. 2009), and that synthetic biology tools make it possible to build non-natural pathways that would be difficult to produce with classic genetic engineering techniques (Pauwels *et al*. 2013). Regardless of whether metabolic pathway engineering is considered a tool of synthetic biology or not, it, nevertheless, relies on *in vitro* nucleic acid techniques, and as such organisms created through its use clearly fall under the definition of LMOs as per the Cartagena Protocol on Biosafety.

Many of the first-wave synthetic biology commercial applications use metabolic pathway engineering to replicate naturally occurring molecules (Wellhausen and Mukunda 2009). The majority of the existing and near-term synthetic biology projects listed in section 4 below falls in this category. Although initial expectations were that synthetic biology metabolic engineering would efficiently produce cheap biofuels, companies have found it easier to enter the commercial markets of higher-value and lower-

12 *Intrexon Corp. (http://dna.com/OurApproach/UltraVector).*

13 *iGEM claims to have changed its evaluation criteria to encourage teams to submit well-characterized and -measured parts. These changes were made in 2011 and are consequently not reflected in the papers referenced. The 2013 iGEM contest website noted significant improvement in the quality of part documentation in the last few years, as well as the continued presence of parts that needed to be discontinued (http://2013.igem.org/Welcome, accessed on 16 Jan. 2014).*

14 *See http://www.biofab.org, accessed on 25 March 2013.*

15 *See http://biofab.synberc.org/content/bootstrapping-biotechnology-engineers-cooperate-realize-precision-grammar-programming-cells, accessed on 19 August 2014.*

volume products, such as cosmetics, pharmaceutical, and specialty chemicals (Hayden 2014; Keasling 2012; WWICS 2012). A major focus of research is on engineering microbes, such as the frequently-used *E. coli* and *Saccharomyces cerevisiae* (baker's yeast), to produce substances such as fuels (such as Amyris' Biofene), medicines (such as Sanofi's semi-synthetic artemisinin), and flavoring/fragrances (such as Evolva's vanillin). Other microorganisms that are a focus of metabolic pathway engineering are microalgae, including the prokaryotic cyanobacteria and eukaryotic algae such as *Chlamydomonas* and *Nannochloropsis*.

3.3. Genome-level engineering

This area of synthetic biology research focuses on the genome as the "causal engine" of the cell (O'Malley *et al*. 2007).[16] Rather than designing short DNA sequences or engineering specific metabolic pathways, researchers work at the whole-genome level. There are two strategies for genome-level engineering: top down and bottom up.

Top-down genome-engineering starts with a whole genome, from which researchers gradually remove non-essential genes to pare it down to the smallest possible genome size at which the cell can continue to function as desired. The primary goal is to craft a simplified "chassis" to which modular DNA "parts" can be added (O'Malley *et al*. 2007; Lam *et al*. 2009). The smaller genome is meant to reduce cellular complexity and thus the potential for unexpected interactions (RAE 2009; Sole *et al*. 2007; Heinemann and Panke 2006). Although the genomes of *E. coli* and *Mycoplasma genitalium* have been successfully reduced by 8 to 21%, many essential genes with unknown functions remain (Lam *et al*. 2009). Porcar and Pereto argue that we are "still far" from a true chassis (2012).

Bottom-up genome-engineering aims to build functional genomes from fragments of synthesized DNA; it is also referred to as "synthetic genomics" (EGE 2009; Garfinkel *et al*. 2007; König *et al*. 2013). Thus far, researchers have reproduced the viral genomes of polio (Cello *et al*. 2002) and the 1918 Spanish influenza (Basler *et al*. 2001; Tumpey *et al*. 2005). In 2010, the J. Craig Venter Institute (JCVI) published the successful synthesis and assembly of the genome of *Mycoplasma mycoides* (1.08 million base pair long), and its transplantation into a *M. capricolum* cell stripped of its genome (Gibson *et al*. 2010). In their article in *Science*, the authors described their work as being in sharp contrast to more classic genetic engineering, because they had produced cells based on computer-designed genome sequences (Ibid.). Furthermore, the first synthetic chromosome of *Saccharomyces cerevisiae* has been synthesized recently (Annaluru *et al*. 2014). Others have pointed out that the synthetic genome was almost entirely copied from an existing genome; *de novo* organisms are not being designed (Porcar and Pereto 2012). Natural genomes are needed as models because many DNA sequences are necessary but have unknown functions. As Gibson *et al*. (2010) acknowledge, there is still no single cellular system in which the biological roles of all of the genes are understood. Still, the authors argue that their success paves the way for synthesizing and transplanting more novel genomes (Gibson *et al*. 2010). And, by assembling the longest genome yet from synthetic DNA, the JCVI researchers' *in vivo* assembly demonstrated a way to bypass the length-limits of DNA synthesis machines (Ma *et al*. 2012).

3.4. Protocell construction

Like the search for a minimal genome, researchers seeking to create a protocell are driven to design for less complexity at the cellular rather than genome level. Protocells have been described as "models of artificial cells that have some properties of living systems but are not yet fully alive" (Armstrong *et al*. 2012). Protocell research aims to create the simplest possible components to sustain reproduction, self-maintenance and evolution (Lam *et al*. 2009; Sole *et al*. 2007). This is understood to require three things: a container or membrane to confine reactions; a metabolism so that energy can be stored; and molecules to carry information in order to adapt to changing environments (EASAC 2010; Sole *et al*. 2007). Research is aiming to achieve compartmentalization through approaches such as lipid-based vesicles, inorganic nanoparticle based membrane vesicles, and membrane-free peptide/nucleotide droplet formation (see Pauwels *et al*. 2013). Cell-free approaches attempt to eliminate cells altogether to provide a more controllable biochemical context for synthetic biology devices (RAE 2009; Pauwels *et al*. 2013).

16 *This section and the next on protocells are sometimes categorized together, and sometimes top-down and bottom-up genomic engineering are separated, but all are commonly included within the scope of synthetic biology.*

Research in this area is vibrant, but thus far restricted to a basic level. Although many protocell scientists are seeking to identify new biotechnology production systems, much protocell research is intended to explore the origin of life (Budin and Szostak 2010; Lim *et al*. 2012; Schmidt 2010). Potential protocell applications include the development of smart "paints" that fix carbon dioxide into inorganic carbonate, chemical agents that convert environmental waste toxins into harmless chemicals, and alternative methods of producing biofuels (Armstrong *et al*. 2012).

3.5. Xenobiology

Xenobiology (also known as chemical synthetic biology) is the study of unusual life forms, based on biochemistry that is not found in nature (Pauwels *et al*. 2012; Schmidt 2010).[17] Xenobiology aims to alter the "biochemical building blocks of life," such as by modifying genetic information to produce xeno-nucleic acids (XNA) or by producing novel proteins (Joyce 2012; Schmidt 2009). One approach to producing XNA is to modify the nucleotide bases of DNA beyond A, G, C, and T, incorporating alternative synthetic nucleotides into DNA (Joyce 2012; Pinheiro and Holliger 2012; Pinheiro *et al*. 2012; Sutherland *et al*. 2013). Candidate bases are being tested for inclusion into DNA with success; Pinheiro *et al*. (2012) engineered six alternative genetic polymers capable of base pairing with DNA and polymerases that could synthesize XNA from a DNA template and reverse transcribe XNA back into DNA. This is not yet a "synthetic genetic system" because DNA is still necessary at multiple points in the process (Joyce 2012), but it shows that synthetic polymers are capable of heredity and Darwinian evolution, meaning "DNA & RNA are not functionally unique as genetic materials" (Pinheiro *et al*. 2012). Another approach to XNA is to replace the "backbone" that the bases connect to or the sugar moiety. Thus, instead of deoxyribonucleic acid (DNA), information is stored via peptide nucleic acids (PNA), glycerol nucleic acids (GNA), and flexible nucleic acids (FNA) (Pinheiro and Holliger 2012). A third approach is to modify the nucleotides' pyrophosphate leaving group (Jang *et al*. 2013). Another area of research is the production of novel proteins that are stable but not found in nature ("never-born-proteins") (Schmidt 2009). There are 20 common amino acids, but researchers have identified in the laboratory over 50 unnatural amino acids that can be incorporated into a peptide (Hartman *et al*. 2007). Recently, a bacterium was produced where one base pair of the original DNA was altered to XNA resulting is the first organism to stably propagate an expanded genetic code (Malyshev *et al*. 2014).

Xenobiology is often cited as a potential built-in biological containment mechanism (see section 7.2) to prevent gene transfer to and from wild organisms (Esvelt and Wang 2013; PCSBI 2010; RAE 2009; Schmidt 2009; Schmidt 2011; Skerker *et al*. 2009). The physical transfer of genetic material might still occur, but in theory natural polymerases would be unable to accurately read the XNA, and would thus not lead to the production of a protein (Schmidt 2009). This goal is often described as producing "orthogonal" systems, where modifying one component does not result in side effects to other components in the system (Moe-Behrens *et al*. 2013; Schmidt 2010). Orthogonality is a foundational property of engineering, and synthetic biologists are attempting to achieve its expression within living systems. Scientists aim at using synthetic biology to achieve two types of orthogonality: first, parts and devices inserted into a cellular chassis may be orthogonal to the chassis' own genome and proteome, which in theory should prevent unpredictable interactions and enhance the predictability of designs; second, organisms resulting from synthetic biology may be orthogonal to the biotic environment in which they are released, which should help prevent horizontal gene transfer as described earlier. This claim, however, is untested as xenobiology is in an early stage of development (Pauwels *et al*. 2012). Furthermore, orthogonality is a property of systems, but there is quite a diverse understanding within synthetic biology of what a system is, and therefore to what extent orthogonality can be attributed to it (Delgado and Porcar 2013). A key issue is whether one chooses to understand the system as a composition of parts, or whether one puts the focus on the relational nature of living systems and their emergent properties. Orthogonality has often been presented as a relative property of natural systems (de Lorenzo 2010a, 2011), and therefore one that can be enhanced by using design approaches in synthetic biology. A question is whether living systems are naturally orthogonal at all, or whether they could be engineered as if they were (Calvert 2010). Many scholars in related disciplines such as systems biology would be skeptical about the idea that synthetic biology can produce systems to work in orthogonal ways or that orthogonality could be engineered as an inherent property of the systems (Noble 2006). This is especially so in sub-fields such as ecology and developmental biology,

17 Joyce (2012) also describes this as "alternative biology."

in which the relational nature of living systems is emphasized and natural complexity is seen as an emerging property of the system, rather than something to be deleted or simplified. In short, that emergence, and unpredictable change and behaviour are what ultimately characterize life itself. König *et al*. (2013) cite the recent Pinheiro *et al*. (2012) work to warn that natural polymerases might be able to evolve to recognize XNA, necessitating additional "firewall levels" to act as a biosafety tool. In their work, Marris and Jefferson (2013) have highlighted additional challenges of orthogonality as an approach to biosafety. Heinemann and Traavik (2004) note that a powerful mechanism of change by horizontal gene transfer (see section 6.2) is through recombination with DNA sequences of low overall DNA similarity. Thus, it can be expected that any potential to pair between unintended xeno-base combinations and the xeno-bases and canonical DNA nucleotides will potentially create new avenues for recombination.

Research in xenobiology is also being used to explore the basic physical properties that led DNA and RNA to be the genetic material of life (Chaput *et al*. 2012; Pauwels *et al*. 2012). It is hoped that xenobiology will be usefully applied to biotechnology and molecular medicine, but "significant research challenges remain" before we see commercial application in this area (Chaput *et al*. 2012; Joyce 2012; Sutherland *et al*. 2013).

4. CURRENT AND NEAR-TERM PRODUCTS INVOLVING SYNTHETIC BIOLOGY

This section provides examples of products *for* synthetic biology and products *from* synthetic biology that are commercially available or near to becoming available on the market.

4.1. Products for synthetic biology

Synthetic oligonucleotides and DNA are widely commercially available. As of 2010, at least 50 companies produce gene-length segments of double-stranded DNA, primarily based in the USA, Germany and China (Tucker 2010). For those who want to synthesize their own oligonucleotides, equipment and reagents are commercially available; used oligonucleotide synthesizers are even available on the internet from laboratories that have switched to purchasing DNA from companies (Garfinkel and Friedman 2010).

The Registry of Standard Biological Parts hosts a collection of open source code for DNA parts following BioBrick™ standards. For amateurs and those who are new to synthetic biology, New England BioLabs Inc. offers the BioBrick™ Assembly Kit, which provides enough restriction enzymes and ligase to carry out 50 reactions for 253 USD.[18] The Kit does not contain DNA parts, but the materials to digest and ligate the parts into one DNA plasmid. The iGEM Foundation holds a repository of the physical DNA of BioBrick™ parts. Each year, they send out a Distribution Kit to iGEM teams containing over 1,000 samples of parts as lyophilized DNA.[19] Registered iGEM teams and laboratory groups can order samples of other parts not included in the Distribution Kit by writing to the iGEM Foundation.[20]

4.2. Products from synthetic biology

Products are categorized below based on the stage at which synthetic biology organisms are used and the products replaced by the synthetic biology versions. The majority of current and near-term commercial and industrial applications of synthetic biology engineer microbes that replicate naturally-occurring or petroleum-based molecules for pharmaceuticals, fuels, chemicals, flavorings and fragrances (Wellhausen and Mukunda 2009). While start-up companies often use the term "synthetic biology," established companies with a history in classic genetic engineering rarely do (WWICS 2010). This can add to the lack of clarity regarding which products are produced using synthetic biology. Many of these products are the result of synthetic DNA-circuits and metabolic pathway engineering; thus some of the comments on previous versions of this document contended that some of these products are the result of classic genetic engineering rather than synthetic biology. Examples of products in this section have been specifically described as synthetic biology by sources such as the Biotechnology Industry Organization and the WWICS synthetic biology project (BIO 2013; WWICS 2010 & 2012).

18 *See: https://www.neb.com/products/e0546-biobrick-assembly-kit, accessed 23 Feb. 2014.*

19 *See: http://partsregistry.org/Help:Distribution_Kits, accessed 6 May 2013.*

20 *See: http://partsregistry.org/Help:Requesting_Parts, accessed 6 May 2013.*

4.2.1. Production of molecules that are otherwise produced from petroleum

The commercially available and near-to-market products in this section are the products of organisms resulting from synthetic biology techniques. The organisms themselves remain in contained industrial settings.

Companies have started to produce fuels such as biodiesel and isobutanol by engineering metabolic pathways in microbes and microalgae. In 2010, Solazyme sold over 80,000 liters of algal-derived marine diesel and jet fuel to the U.S. Navy, and have an on-going contract with the U.S. Department of Defense for marine fuel.[21] Amyris' "Renewable Diesel", which is based on Biofene produced by yeast, is used by approximately 300 public transit buses in Sao Paulo and Rio de Janeiro, Brazil.[22] In 2012 Synthetic Genomics, Inc. purchased 81 acres in a south California desert near the Salton Sea to scale up and test algal strains in open ponds for the production of fuel (Synthetic Genomics, Inc. 2012). Calysta Energy™ converts methane and other components of natural gas into liquid hydrocarbons that can be used to make fuels and chemicals. Calysta engineered the metabolic pathways of methanotrophs (methane-using bacteria), using what it describes as synthetic biology.[23]

Chemicals previously produced using synthetic chemistry are now being produced using synthetic biology. Predictions within the chemical industry are that about two-thirds of organic chemicals derived from petroleum could be produced from "renewable raw materials" (BIO 2013). DuPont Tate and Lyle BioProducts have been producing Bio-PDO™ (1,3-propanediol) since 2006, using corn as feedstock and proprietary microorganisms.[24] The same company, in partnership with Genomatica, produced more than 2,000 metric tons of 1,4-butanediol (BDO) in 2012 using engineered *E. coli*.[25] Myriant's production facility in Louisiana, USA was scheduled to start production in 2013 of bio-succinic acid, planning on 30 million pounds of bio-succinic acid annually from microorganisms with altered metabolic pathways (BIO 2013; Myriant undated).[26]

A growing interest in bioplastics has resulted in many systems of production, some of which employ synthetic biology. Metabolix's proprietary microbes use sugar to create biopolymers on a commercial scale (BIO 2013).

4.2.2. Production of naturally-occurring molecules

The commercially available and near-to-market products in this section are the products of organisms resulting from synthetic biology techniques. The organisms themselves are intended to remain in contained industrial settings. Synthetic biology is being explored as an alternative source of such products because naturally-occurring products are expensive to produce using traditional chemical synthesis and/or require relatively large quantities of their natural source (Erickson *et al*. 2011).

"Major flavor and fragrance houses such as Givaudan, Firmenich, and International Flavors and Fragrances [IFF] are intrigued by the possibility of using biotechnology to produce key components of essential oils from abundant sugar feedstocks via fermentation," according to a 2012 article in Chemical and Engineering News (Bomgardner 2012). Allylix[27] and Isobionics[28] are two companies employing synthetic biology to produce synthetic bio-based versions of valencene (orange) and nootkatone (grapefruit) (Bomgardner 2012; WWICS 2012). In 2013, IFF and Swiss-based Evolva entered into pre-production phase of what they describe as "natural vanillin" from yeast-based fermentation (IFF and Evolva 2013). As of early 2014, this vanillin is anticipated to be the "first major synthetic-biology food additive to hit supermarkets" (Hayden 2014). Some claim that, because the vanillin is produced by a living organism (the engineered yeast) and the yeast is not present in the final product, it can be described as "natural" and, in some cases, depending on the specific regulatory framework, it may not be required to be labeled in any particular way (Hayden 2014). Evolva is using similar synthetic-biology based processes in its research and development of key saffron components and stevia (WWICS 2012).[29]

21 See http://solazyme.com/fuels, accessed 4 June 2013.

22 See: http://www.amyris.com/Content/Detail.aspx?ReleaseID=166andNewsAreaID=21andClientID=1, accessed on 10 May 2013.

23 See: http://www.calystaenergy.com/technology.html, accessed 22 Jan. 2014.

24 See http://www.duponttateandlyle.com, accessed 5 June 2013.

25 See http://www.genomatica.com, accessed 5 June 2013.

26 The Biotechnology Industry Organization's (BIO) comments on an earlier draft of this document pointed out Myriant bio-succinic acid as not produced by synthetic biology ("Myriant's bio-succinic acid is produced by an organism that contains no foreign DNA and was generated by standard techniques of gene deletion and selection for faster growing natural mutants. No "Synthetic Biology" was used.") The BIO (2013) document "Current Uses of Synthetic Biology for Renewable Chemicals, Pharmaceuticals, and Biofuels" identifies Myriant's bio-succinic acid as a product of synthetic biology, as does WWICS (2012).

27 See http://www.allylix.com, accessed 6 June 2013.

28 See http://www.isobionics.com, accessed 6 June 2013.

29 See http://www.evolva.com/products/saffron, accessed 6 June 2013.

Synthetic biology production of otherwise naturally sourced molecules for cosmetics and personal care products are coming onto the market, too. Squalene, an emollient, has historically been sourced from the livers of deep sea sharks although recently plant-based alternatives have become available (ETC 2013a; WWICS 2012). In 2011, Amyris brought a synthetic biology-produced squalane[30] to the Japanese market, marketed as Neossance™ Squalane. Using Brazilian sugarcane as feedstock, Amyris modified yeasts to produce the hydrocarbon farnesene, which can be finished as squalane (WWICS 2012; Centerchem undated). In September 2013, Solazyme and Unilever signed a commercial supply agreement for an initial supply of at least 10,000 metric tons of Solazyme Tailored™ Algal Oil (Solazyme 2013). Unilever reportedly plans to use the oil for its personal care products (Cardwell 2013).

Perhaps the most famous pharmaceutical produced using synthetic biology techniques is the anti-malarial semi-synthetic artemisinin. In 2013, Sanofi started producing a yeast that was genetically engineered to produce artemisinic acid (see section 10). It is as yet unclear whether the synthetic production will complement or replace the thousands of small-scale farmers of *Artemisia* sp., the natural source of artemisinin, in Asia and Africa (Sanofi and PATH 2013; ETC 2013a). The issues raised by the production of semi-synthetic artemisin go deeper that an evaluation of the balance between the health benefits to populations in countries affected by malaria and the potential loss of income and livelihoods for farmers growing *Artemesia* bushes as a crop. A crucial issue is that the claimed or hoped-for health benefits for local populations do not simply depend of an increased supply of artemisisin (synthetic or not), but also requires a complex set of interrelated political, economic and social conditions (Marris 2013).

Shikimic acid is another example of naturally-occurruing molecule being produced with synthetic biology tools. The popular anti-influenza drug Tamiflu, which rose in importance during the swine flu pandemic, is made from shikimic acid traditionally sourced from the star anise plant. The pharmaceutical company La Roche started producing shikimic acid via fermentation by engineering the metabolic pathway of bacteria. The ETC Group identifies this process as synthetic biology (ETC 2013a) and Rawat *et al*. (2013) described it as "rational strain design by metabolic pathway engineering".

Many other naturally-occurring molecules are expected to be produced in agricultural crops through the use of "precision genome engineering" which combines classic genetic engineering with some techniques of synthetic biology. Voytas and Gao (2014) have recently published a paper discussing the opportunities and regulatory challenges of precision genome engineering.

4.2.3. Industrial and pharmaceutical use of organisms resulting from synthetic biology techniques

Synthetic biology is being used in an attempt to design cheaper and more efficient industrial systems of production, potentially providing savings in energy use, reduced toxic waste products, and reduced use of chemicals for processing (BIO 2013; Erickson *et al*. 2013). For example, the pharmaceutical company DSM Sinochem introduced and optimized two genes into a penicillin-producing microbial strain, making a process for producing the synthetic antibiotic cephalexin that they claim to be faster, cheaper, and less energy-intensive (Erickson *et al*. 2011).

Enzymes modified by synthetic biology techniques are being explored and used for the production of pharmaceuticals and biofuels. For example, Januvia©, a medicine for type II diabetes, is produced by Merck using an enzyme modified by synthetic biology techniques by Codexis (BIO 2013).

4.2.4. Commercially available micro-organisms resulting from synthetic biology techniques

In this category, organisms resulting from synthetic biology techniques are themselves for sale. These micro-organisms resulting from synthetic biology techniques are largely marketed for their ability to produce specific desired chemicals, and thus seem to be intended for contained industrial uses.

New companies are starting to offer "made to order" microorganisms, produced in part using synthetic biology. For example, Ginkgo BioWorks™[31] promises "scale-up-ready organisms in six months" for customers such as sugar refiners, flavor and fragrance companies, and other producers of fine chemicals. Ginkgo BioWorks™ uses a "proprietary CAE (Computer-Aided Engineering) suite to produce organisms designed to specification," including proprietary DNA assembly technology and CAM (Computer-Aided Manufacturing) tools to fabricate and analyze candidate organisms. Tom Knight, co-creator of BioBricks™, is a co-founder of Ginkgo

30 *Squalene is the natural compound, and squalane is the hydrogenated form of the compound. Squalane is more commonly used in cosmetics and as a lubricant.*

31 *See: http://ginkgobioworks.com/tech.html, accessed 6 March 2013.*

BioWorks™. While open-source BioBricks™ are restricted to three combinations in one reaction, Knight's redesigned system for proprietary use can reportedly combine up to 10 parts in one reaction (Baker 2011). Ginkgo BioWorks™ advertises its customers as including DARPA (the US Defense Advanced Research Projects Agency), NIST (the US National Institute of Standards and Technology), and ARPA-e (the US Advanced Research Projects Agency – Energy).[32]

4.2.5. Commercially available multi-cellular organisms resulting from synthetic biology techniques

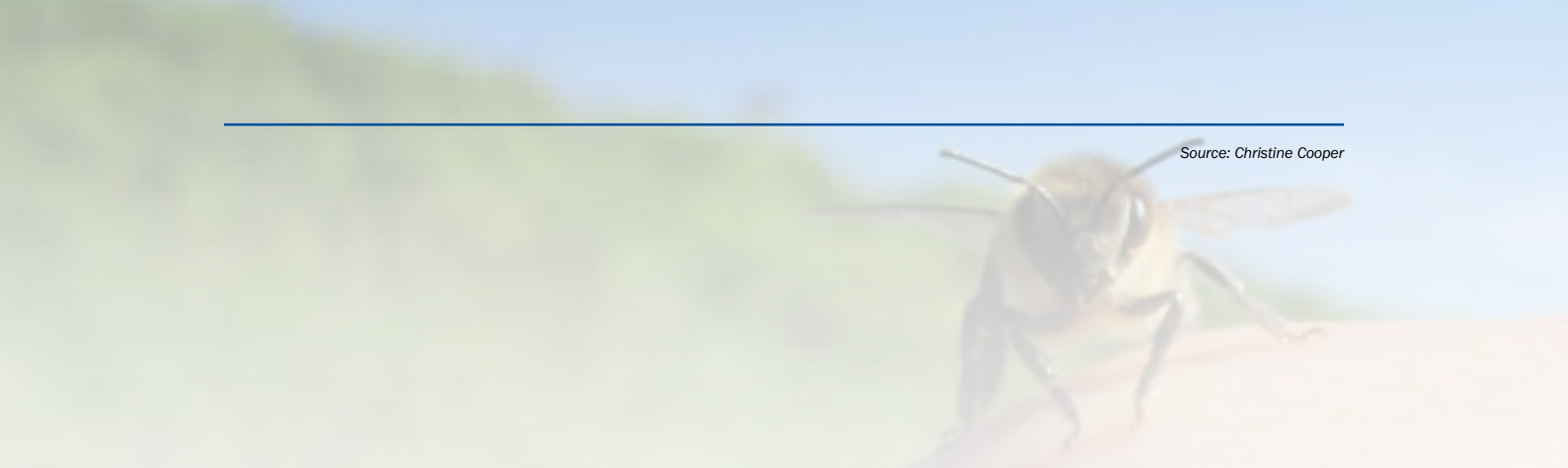
In this category, multi-cellular organisms resulting from synthetic biology techniques are being developed for release on the market. No multi-cellular organism appears to be currently on the commercial market. The prospective uses in this category are intended for environmental release.

Agricultural crops are being developed with genes modified using synthetic biology technology, intended as feedstock for biofuels. Agrivida, Inc. uses proprietary INzyme™ technology, described by the Biotechnology Industry Organization (BIO) as a "novel approach to synthetic biology," to grow biomass feedstock with dormant biodegrading enzymes that are activated after harvest with the aim of reducing the cost and energy of breaking down feedstock for the fermentation process to produce ethanol (BIO2013). In June 2012, Agrivida, Inc. announced that it had launched its "first significant field production" of modified corn in US Department of Agriculture-permitted field trials (Agrivida 2012). It should be noted that, while others use the term synthetic biology to describe the technology used to design and engineer the enzyme sequences (BIO 2013; Lipp 2008; Schmidt 2012), Agrivida does not, instead using terms such as engineering; an example of the lack of clear boundaries between classic genetic engineering and synthetic biology.[33] Similarly, Syngenta's Enogen corn contains alpha amylase enzyme in its endosperm with the aim of facilitating ethanol production. The ETC Group (2013) lists it as an application of synthetic biology, but Syngenta does not use the term 'synthetic biology' in describing its design and production (Syngenta 2012).

32 See: http://ginkgobioworks.com/partner.html, accessed 23 March 2013.

33 See also: http://www.agrivida.com/technology/overviewtechnology.html, accessed 4 February 2014.

Source: Macroscopic Solutions, LLC



Source: Christine Cooper

D. POTENTIAL IMPACTS OF THE COMPONENTS, ORGANISMS AND PRODUCTS RESULTING FROM SYNTHETIC BIOLOGY TECHNIQUES ON THE CONSERVATION AND SUSTAINABLE USE OF BIOLOGICAL DIVERSITY

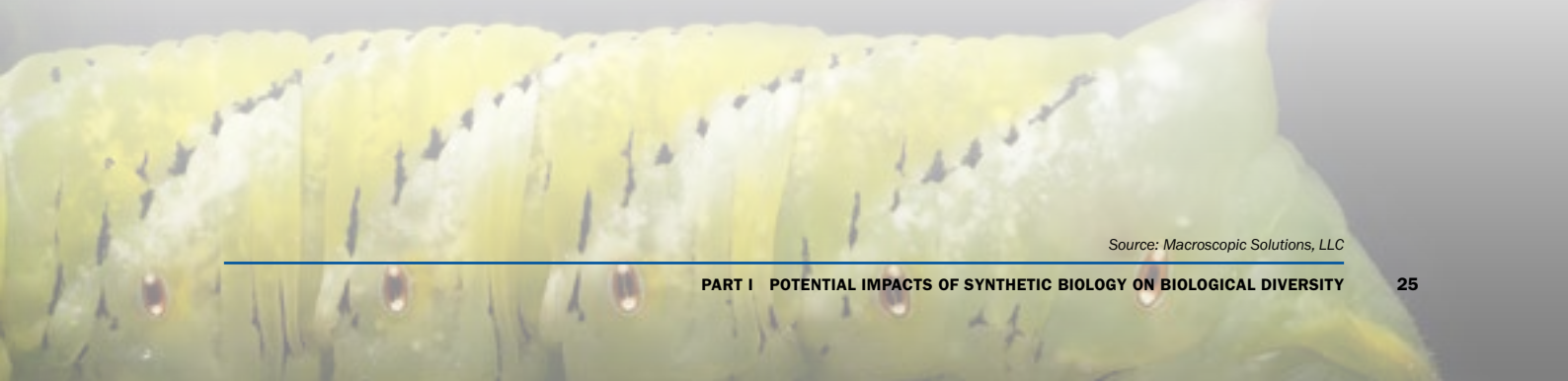
The conservation of biodiversity is one of three primary objectives of the CBD. The CBD's text defines *ex situ* conservation as "the conservation of components of biological diversity outside their natural habitats," and *in situ* conservation as "the conservation of ecosystems and natural habitats and the maintenance and recovery of viable populations of species in their natural surroundings and, in the case of domesticated or cultivated species, in the surroundings where they have developed their distinctive properties" (CBD, Art 2). The conservation of biological diversity occurs at all levels: genes, species and ecosystems.

Furthermore, in the context of the CBD, sustainable use is defined as "the use of components of biological diversity in a way and at a rate that does not lead to the long-term decline of biodiversity, thereby maintaining its potential to meet the needs and aspirations of present and future generations" (Art. 2). Sustainable use encompasses ecological, economic, social, cultural, and political factors (Glowka *et al*. 1994).

5. APPLICATIONS OF SYNTHETIC BIOLOGY AND THEIR POTENTIAL POSITIVE AND NEGATIVE IMPACTS

Although synthetic biology is often referred to as a coherent and single discipline presenting uniform benefits and dangers, the different areas of synthetic biology research represent different potential impacts, both negative and positive, on biodiversity-related issues.

This section discusses the potential impacts of components, organisms and products resulting from synthetic biology techniques on the conservation and sustainable use of biodiversity. A number of specific areas of current and potential applications of synthetic biology are described along with potential positive and negative impacts of these applications on the conservation and sustainable use of biodiversity. Table 1 at the end of this section summarizes examples of the potential positive and negative impacts of synthetic biology applications on conservation and sustainable use of biodiversity. Biosafety concerns of a more general nature are examined in section 6.



Source: Macroscopic Solutions, LLC

5.1. Bioenergy applications

Bioenergy applications, particularly through fuel production, are a significant focus of synthetic biology research (WWICS 2013a). As discussed above (section 4.2.1), biofuels produced using synthetic biology techniques are beginning to reach the stages of field testing, pilot runs, and relatively small-scale production. One area of research is to use synthetic biology tools to develop enzymes that break down a wider range of biomass more effectively, making it possible to utilize agricultural waste such as corn stalks and straw, and woody biomass (PCSBI 2010). Other approaches are to use synthetic biology to develop plants with more readily convertible biomass, or to engineer photosynthetic algae (including microalgae such as cyanobacteria) to produce more bio-oil (Georgianna & Mayfield 2012; PCSBI 2010). One goal of synthetic biology energy research is the production of consolidated bioprocessing platforms, such as *E. coli* engineered to both degrade biomass (without the external addition of enzymes) and convert biomass into biofuels (Bokinsky *et al*. 2011). The UKSBRCG (2012) describes synthetic biology research towards producing an artificial leaf that could convert solar energy into a carbon-based liquid fuel. The PCSBI (2010) describes synthetic biology research towards producing hydrogen fuel, from engineered algae to using starch and water via a synthetic enzymatic pathway. Synthetic biology tools are also expected to help design ways to harvest currently inaccessible hydrocarbons, such as coal bed methane (PCSBI 2010).

Claims that there could be significant benefits for biodiversity from replacing fossil fuel energy sources with bioenergy are based on the premise that these approaches could reduce global dependence on fossil fuels and cut harmful emissions at a significant scale (PCSBI 2010). Through the CBD's cross-cutting programme on climate change and biodiversity, CBD bodies have documented and assessed the interlinkages between the two areas.[34] Synthetic biology tools may be used in designing "next generation" biofuels that, it is hoped, will overcome challenges of "first generation" biofuels made from food crops (Webb & Coates 2012).

Potential negative impacts could result from the increased utilization of biomass for synthetic biology applications. "Biomass" is generally used to refer to the use of "non-fossilized biological and waste materials as a feedstock" (ETC 2011). Much synthetic biology research aims at designing organisms that will use biomass as feedstock to produce fuels, chemicals, and pharmaceuticals at greater efficiencies than have previously been possible (PCSBI 2010). For example: Solazyme (see above) uses heterotrophic algae, i.e. algae that are able to feed on sugar for their energy source rather than utilizing sunlight to produce sugar through photosynthesis. The advantage of heterotrophic algae is that they yield more oil but the clear disadvantage is they have to be fed, in this case with sugar, which in turn has to be sourced from biomass grown on land. Some products, such as biofuels, are relatively low-value and high volume, and thus would require large amounts of biomass. As described in *CBD Technical Series 65: Biofuels and Biodiversity*, there are contradicting studies on the sustainability of utilizing waste feedstocks such as corn stover and straw (Webb & Coates 2012). A number of studies in ecology, agronomy, and environmental history find that biomass extraction from existing agricultural practices is already leading to a decline in soil fertility and structure (Blanco-Canqui and Lal 2009; Wilhelm *et al*. 2007; Smil 2012). Studies done in the US have found that removing corn stover from fields would require significant additional use of nitrogen, phosphorous and potassium fertilizers (Blanco-Canqui and Lal 2009; Fixen 2007). In addition to the potential loss of ecological functions of the soil biomass, there is also concern around the social impacts of increased biomass removal. Some civil society groups are concerned that, in part due to increased demand from synthetic biology, the tropics and sub-tropics will be targeted for their biomass and lead to economic and environmental and cultural injustice (ETC 2010; FOE *et al*. 2012; FOE 2010). They predict that communities will lose local access to resources, sustainable uses will be displaced, and environmental harm will be caused by establishing plantations in former forests, harvesting natural grasslands, and placing pressures on "marginal" lands such as deserts and wetlands (ETC 2010). While synthetic biology techniques promise to open up new sources of energy, such as algae and seaweed, the ETC Group has expressed concern that these uses will encroach on coastal and desert ecosystems and their traditional uses (ETC 2013). The US PCSBI noted: "On balance, many anticipate the potential efficiencies and attendant reduction in reliance on fossil fuels offered by energy production using synthetic biology would offset anticipated risks to the environmental ecosystem as it exists today. But considerable uncertainty remains" (PCSBI 2010).

As will be discussed in more detail in section 6, there are biosafety considerations related to the accidental or intentional release of organisms resulting from synthetic biology techniques used for bioenergy purposes. For example, microalgae resulting from synthetic biology techniques for bioenergy purposes

34 See: http://www.cbd.int/climate, accessed 13 Feb. 2014.

may have ecological impacts, particularly if grown in open ponds and thus with a higher chance of accidental release (Snow & Smith 2012). Moreover, micro-organisms may be used in small-scale decentralized bioreactors (e.g. for production of biofuels on farms), and this could be considered to constitute a new kind of category in-between contained use in large industrial fermenters and full deliberate release. Marris and Jefferson (2013) argued that there are blurred boundaries between contained use and deliberate release of genetically modified micro-organisms (GMMO), and "these boundaries are likely to be further challenged if and when the GMMO applications envisaged by synthetic biologists for environmental, agricultural and mining uses enter the regulatory system, because those applications cover a whole spectrum in terms of the nature, scale, and time-horizon of the release".

5.2. Environmental applications

Another area of synthetic biology research is in environmental applications, most of which would require environmental release or contained use[35] outside of the laboratory of organisms resulting from synthetic biology techniques. Scientists anticipate the use of engineered microbial consortia, in part using tools of synthetic biology, to enhance mining metal recovery and to aid in acid mine drainage bioremediation (Brune and Bayer 2012). Synthetic biology techniques are being used to design whole-cell biosensors that will indicate the presence of a target, such as arsenic in drinking water. French *et al*. (2011) describe their work growing out of an iGEM project to design an arsenic biosensor that would be suitable for field use in developing countries, using freeze-dried transformed *E. coli* that change color in the presence of arsenic. The arsenic biosensor work is now being further developed by the "Arsenic Biosensor Collaboration" (http://arsenicbiosensor.org). In another example of an environmental application, the 2011 European Regional Jamboree winning iGEM project involved engineering *E. coli* to secrete auxin, a plant hormone intended to promote root growth. The Imperial College (UK) team proposed pre-coating seeds with the bacteria, to be planted in areas at risk from desertification.[36]

Since recombinant DNA technology was first introduced, the use of genetically engineered micro-organisms for bioremediation and other environmental applications "has been a holy grail" – much desired but constantly out of reach (Skerker *et al*. 2009). Synthetic biologists see the failure to deliver the anticipated or desired benefits as due to the lack of sophistication of classic genetic engineering techniques (Marris and Jefferson 2013). As a result, synthetic biologists are generally optimistic about the potential for synthetic biology to succeed where previous modified micro-organisms for environmental release have failed (Garfinkel and Friedman 2012; PCSBI 2010; Schmidt and de Lorenzo 2012; Skerker *et al*. 2009). If so, synthetic biology could provide less toxic and more effective tools for bioremediation, which would positively impact local biodiversity.

If synthetic biology succeeds in producing microbes that are sufficiently hardy for release into the environment, such microbes may raise significant biosafety concerns depending on their potential to survive and persist (König *et al*. 2013), as well as on their potential to interact with their immediate environment causing adverse effects. Some of these micro-organisms might present significant challenges for the risk assessment approaches that are currently in use by regulatory processes (see section 6). The WWICS Synthetic Biology Project held several workshops on aspects of the safety of environmental release of organisms resulting from synthetic biology, identifying key areas of uncertainty and areas for research, and discussing what "safety" means in the context of synthetic biology (see WWICS 2013b for notes from workshops from 2000 to 2012). One question is how an organism designed for environmental release can be robust enough to accomplish its intended task but not persist and become problematic (Anderson *et al*. 2012). Those optimistic about the role of microbes resulting from synthetic biology techniques tend to acknowledge the possibility of invasiveness and unintended effects, but they also invoke the (not yet realized) promise of xenobiology and other orthogonal systems with built-in biological containment measures (Marris and Jefferson 2013; PCSBI 2010; Schmidt and de Lorenzo 2012; Skerker *et al*. 2009).

35 *"Contained use", as defined in the Cartagena Protocol on Biosafety, article 3, paragraph (b), means any operation, undertaken within a facility, installation or other physical structure, which involves living modified organisms that are controlled by specific measures that effectively limit their contact with, and their impact on, the external environment.*

36 *See http://2011.igem.org/Team:Imperial_College_London, accessed on 5 June 2013. The team developed a bio-cotainment strategy ("Gene Guard") intended to prevent horizontal gene transfer, in response to concerns about the release of their organism into the environment. As French et al. (2011) explain, iGEM projects may not be as well-characterized as experiments reported on in peer-reviewed literature, but they are often based on highly creative ideas and can presage possible future applications in areas of synthetic biology. For this reason, they are often referenced when the powerful possibilities of synthetic biology are discussed. Dana et al. (2012) cite this project in their article on designing appropriate biosafety systems for synthetic biology.*

5.3. Applications to alter wildlife populations

Synthetic biology techniques are being explored for their potential to alter wildlife populations for conservational, health and agricultural purposes. Such potential uses of synthetic biology could have positive impacts on the health of humans, wildlife and ecosystems. The 2013 conference "How will synthetic biology and conservation shape the future of nature?" and an article in *PLOS Biology* (Redford *et al*. 2013) has sparked conversation between synthetic biologists and conservationists. At the conference, ideas for potential synthetic biology projects for conservation were identified, including adapting coral to temperature and acidity, attacking the fungus that causes white-nose syndrome in bats, and finding solutions to the crashing of bee populations.[37] Redford *et al*. (2013) suggest that synthetic biology applications in agriculture and bioenergy could alleviate pressure on ecosystems, aiding conservation. Furthermore, specific species or populations of wildlife may also be the target of synthetic biology applications to eradicate or control populations. For example, synthetic biology could be used to create "gene drive" systems that may be used to spread traits to control diseases borne by insect vectors, such as mosquitoes, by suppressing populations, potentially to the point of extinction (Weber and Fussenegger 2012) similar to what has been done by Oxitec to produce genetically modified mosquitoes with the aim of controlling dengue fever carriers.[38] Researchers have introduced a synthetic homing endonuclease-based gene drive system into mosquitoes in the laboratory, which could be used to increase the transmission of genetic modifications to wild populations of mosquitoes (Windbichler *et al*. 2011). Regarding the use of endonuclease-based gene drive systems to alter populations, Esvelt *et al*. (2014) hypothesize that this technique could also be used, for example, to restore vulnerability to pest and weeds which have acquired resistance to pesticides and herbicides by replacing the resistance genes with their ancestral forms, and to promote biodiversity by controlling or even eradicating invasive species. Concerns arising from the use of gene-drive systems to alter wild populations are raised by Esvelt *et al*. (2014) and Oye *et al*. (2014), who also propose possible risk management options before the development of any actual RNA-guided gene drives. As suggested by Oye *et al*. (2014), for emerging technologies that affect the global commons, concepts and applications should be published in advance of construction, testing, and release. This lead time would enable public discussion of environmental and security concerns, research into areas of uncertainty, and development and testing of safety features. It would also allow adaptation of regulations and conventions in light of emerging information on benefits, risks, policy gaps, and, more importantly, it would allow broadly inclusive and well-informed public discussion to determine if, when, and how gene drives should be used. There would also be biosafety considerations, including negative impacts on the health of humans, wildlife and ecosystems, relating to the use of organisms resulting from synthetic biology techniques designed for environmental release (section 6).

Popular press has given significant attention to the project of "de-extinction", which could involve synthetic biology techniques, along with advanced cloning and other tools of modern biotechnology. De-extinction was the subject of a day-long TEDx conference in Washington, DC (USA), and was the cover story of *National Geographic* in March 2013.[39] Research around the world is underway to restore extinct species such as the passenger pigeon, woolly mammoth, and the gastric brooding frog. Some (but not all) of the work towards bringing extinct species back to life involves techniques of synthetic biology, such as synthetic genome engineering. At the TEDx conference, George Church described innovations in DNA delivery and directed splicing into existing genomes to adapt the genomes of existing species to produce the physiological traits of the extinct species, such as tusks and woolly hair (Church 2013). It must be noted that de-extinction initiatives will only succeed if and when the decades-old challenges of cloning are overcome (Campbell 2004). Although de-extinction has not yet been achieved beyond viruses, conservationists and synthetic biologists are starting to discuss the potential impacts on biodiversity and ecosystems (Friese and Marris 2014).

Some conservationists anticipate positive direct and indirect ecological benefits from de-extinction. Stewart Brand, president of the Long Now Foundation, has argued that restoring keystone species such as woolly mammoths would help restore ecological richness as well as serve as flagship species to inspire ecosystem protection (Brand 2013a). Stanley Temple sees a potential use in reviving extinct alleles

37 *For an overview of the meeting, see Rob Carlson's blog "Harry Potter and the Future of Nature" at http://www.synthesis.cc/2013/05/the-economics-of-artemsinin-and-malaria.html, accessed on 5 June 2013.*

38 *Oxitec's ongoing field trials of OX513A Aedes aegypti: http://www.oxitec.com/health/our-products/aedes-agypti-ox513a/ongoing-field-trials-of-ox513a-aedes-aegypti/.*

39 *The webcast of the 15 March 2013 conference is accessible at: http://longnow.org/revive/tedxdeextinction, accessed on 15 March 2013.*

of species whose genetic diversity is dangerously low, or when "we've solved the issue that caused them to go extinct" (Temple 2013). Restoration of certain species could help restore ecosystems that rely on the ecological functions of those species (Seddon *et al*. 2014). Among possible indirect impacts, some are hopeful that the promises of synthetic biology and de-extinction will provide a new paradigm for biodiversity-advocacy, replacing crisis with a message of hope (Anderson 2013; Brand 2013; Burney 2013; Redford 2013). Kent Redford argues that conservation biology started as a "crisis discipline", and that after 30 years people have "stopped listening." His lesson from this is that "hope is the answer: hope is what gets people's attention" (Redford 2013). Similarly, David Burney describes his "poor man's Jurassic Park" efforts at re-wilding abandoned agricultural land as "trafficking in a very rare and valuable commodity in conservation: hope" (Burney 2013).

The use of synthetic biology for de-extinction projects and, more broadly, conservation projects also raises concerns. As discussed more fully in section 6, there is the possibility of direct negative impacts on biodiversity, such as organisms resulting from synthetic biology techniques becoming invasive or negatively affecting host ecosystems.[40] There is also concern about indirect impacts of the promises of synthetic biology and de-extinction such as co-evolution of other organisms (including pathogens, parasites, symbionts, predators, prey/food, co-inhabitants, commensalism, etc.) and diseases. A prominent concern among conservationists is that the hunt for synthetic biology solutions will divert focus, significant funds and other resources from other conservation efforts (Ehrenfeld 2013; Ehrlich 2014; Pimm 2013; Temple 2013). The editors of *Scientific American* warn that de-extinction "threatens to divert attention from the modern biodiversity crisis" (Editors, 2013). Stuart Pimm points out that his work with poor people in Brazil and Madagascar does not generate money for his university, unlike that of molecular biologists, and that de-extinction "can only perpetuate" the trend of university de-investment in ecology and field biology while "seduc(ing) granting agencies and university deans into thinking they are saving the world" (Pimm 2013). These concerns about diversion of resources from other conservation efforts are particularly keen because of the speculative nature of de-extinction projects and their high price tags (Ehrenfeld 2013; Ehrlich 2014). In comments to an earlier draft of this document, one organization noted that, outside of synthetic biology and conservation communities, publicity around de-extinction has prompted research policy communities to consider responsible conduct of research and prioritization of research areas. Another concern is that support for *in situ* conservation may decrease with the expectation that extinct species will be resurrected (ICSWGSB 2011; ETC 2007; Ehrenfeld 2013; Norton 2010; Pimm 2013; Redford *et al*. 2013; Temple 2013). Biologist David Ehrenfeld (2013) worries about what happens "when Members of Congress think it (extinction) is just a bump in the road?" Conservation biologist Stanley Temple (2013) notes the possibility that de-extinction research may have a de-stabilizing effect on conservation, leading to a net loss as less charismatic species are allowed to slip away. In an editorial in *PLoS Biology*, Redford *et al*. (2013) describe the potentially reduced willingness to conserve endangered species as a "moral hazard" of de-extinction research.

5.4. Agricultural applications

There are hopes that synthetic biology tools and techniques will advance agricultural efficiency and lessen negative environmental impacts of agricultural production. The *UK Synthetic Biology Roadmap* predicts that "Synthetic biology has the potential to make food crops less vulnerable to stresses such as drought, saline water or pests and diseases; and/or to create new plants that can produce, in the field, large volumes of substances useful to man" (UKSBRCG 2012). In 2009, the RAE (2009) anticipated that, within 10 years, synthetic biology would be used to engineer new types of pesticides that are "very specific" and do not persist in the environment past their usefulness. The US PCSBI (2010) anticipates high yield and disease resistant feedstocks that can be supplemented with micro-organisms to minimize water use and replace chemical fertilizers. A columnist for *The Guardian* enthusiastically wrote that: "Current GM crops are the Ford Cortinas of agriculture, but synthetic biologists aim to make Ferrari plants that perform photosynthesis more efficiently by harvesting light from wider regions of the spectrum, or even capture nitrogen directly from the air so

40 *Redford et al. (2013) acknowledge the possibility of novel organisms becoming invasive or affecting the integrity of the host ecosystem. A professor of biotechnology, Subrat Kumar, recently wrote in Nature that the risk of a revived extinct species becoming invasive "are negligible compared with the scientific and social benefits of reviving the lost species" (Kumar 2013).*

Source: Macroscopic Solutions, LLC

they won't need nitrogen fertiliser" (McFadden 2012). There also hopes that the use of synthetic biology in agricultural production sectors will foster "sustainable intensification" and thus reduce land conversion into farmland and increase protection of wild habitats (Redford *et al*. 2013). There are hopes that synthetic biology can be used to design plants to serve as feedstocks for micro-organisms that would need less chemical pesticides and fertilizers, which could have positive ecological impacts (PCSBI 2010). These examples all relate to potential applications of synthetic biology to agriculture. Thus far, it is unclear whether there are commercialized agricultural applications of synthetic biology.[41]

Possible applications of synthetic biology for agriculture could also lead to negative impacts on biodiversity. As with other potential future applications of synthetic biology, many of the potential synthetic biology projects for agriculture would involve the release of organisms resulting from synthetic biology techniques. As discussed in section 6, this could lead to the possibility of negative impacts at an ecological level (such as organisms resulting from synthetic biology techniques becoming invasive, disrupting food webs or having other negative effects on non-target species) or through the transfer of DNA from vertical or horizontal gene flow (König *et al*. 2013; Wright *et al*. 2013). If and when these applications near commercialization, a rigorous, science-based evaluation of the potential impacts would be needed on a case-by-case basis (see section 8).

5.5. Applications to replace natural materials

Synthetic metabolic engineering and DNA-based device construction are being used to produce chemicals and molecules that are otherwise sourced from wild and cultivated plants and animals. Groups from industry and civil society have pointed to potential positive and negative impacts on biodiversity. Applications that are on the market or near commercialization are mostly the result of synthetic metabolic pathway engineering, and therefore are not universally recognized as resulting from synthetic biology techniques. Moreover, it should also be noted that these processes involve micro-organisms not meant to be intentionally released into the environment (although risks of unintentional release may still apply, as discussed in section 6).[42]

Molecules produced through synthetic biology could promote the conservation of plants and animals that are currently unsustainably harvested from the wild or through unsustainable cultivation. One possible example is squalene, an emollient used in high-end cosmetics and personal care products that has historically been sourced from the livers of deep sea sharks (ETC 2013a; WWICS 2012). In recent years, plant-based squalene, primarily from olives, became available as an alternative source to sharks. Unilever has already replaced squalene from sharks with the plant-based version in response to a campaign by Oceana to preserve deep sea sharks. Companies point to the price volatility and limited availability of the squalene sourced from olives, and some manufacturers continue to use deep sea sharks,[43] according to a French NGO (BLOOM 2012; Centerchem undated). In 2011, Amyris brought a synthetic biology-produced squalene to the Japanese market, marketed as Neossance™ squalane[44]. Using Brazilian sugarcane as feedstock, Amyris transformed yeasts to produce the hydrocarbon farnesene, which can be finished as squalene (WWICS 2012; Centerchem undated). Synthetic biology-produced squalene could potentially help to ease pressure on deep sea shark populations. Another example is palm oil, one of the industrial uses of which is to manufacture surfactants. The Biotechnology Industry Organization (2013) references concerns with the production of oil palm harming rainforest ecosystems, and points to industrial synthetic biology research to convert agricultural waste materials (soybean hulls) into surfactants.

The replacement of natural products with products resulting from synthetic biology could lessen the pressure on natural habitats but could also disrupt *in-situ* conservation projects. For example, Evolva and International Flavors and Fragrances, Inc. plan to market their vanillin, which is produced through fermentation in yeast (see section 4.2.2), as a natural product in the EU,[45] and hope to have a competitive advantage over other synthetic forms of vanillin, which are currently produced from

41 *As discussed in section 4.2.5, crops have been engineered with enzyme sequences in order to break down the feedstock for fermentation in making biofuels. Whether the techniques used to design and engineer the enzymes are indeed "synthetic biology" is a point of contention (BIO 2013; Lipp 2008; Schmidt 2012).*

42 *Many national biosafety frameworks regulate these micro-organisms under provisions for GMOs/LMOs destined for contained use.*

43 *According to Oceana's website: http://oceana.org/en/our-work/protect-marine-wildlife/sharks/learn-act/shark-squalene, accessed 21 March 2013.*

44 *Squalene is the natural compound, and squalane is the hydrogenated form of the compound. Squalane is more commonly used in cosmetics and as a lubricant.*

45 *On their website, Evolva states: "Recent EU regulatory changes have strengthened the competitive advantage of the proposed product. New EU rules state that only substances or preparations derived directly from an animal or vegetable material may be labelled "natural". Available at: http://www.evolva.com/products/vanilla, accessed on 21 March 2013.*

petrochemicals and paper pulp. While the developers of vanillin claim that their product offers the world a clear alternative to the petrochemical variety of vanillin without introducing a new environmental threat to rainforests and endangered species, the ETC Group warns that its large-scale production could negatively impact the many small-scale farmers involved in the production of cured vanilla beans (ETC 2013a). Vanilla orchids are commonly produced by inter-cropping with rainforest trees as 'tutors' for vanilla vines to grow on. ETC Group is concerned that this agro-ecological method of cultivation and livelihood for an estimated 200,000 people could be disrupted (ETC 2013a). ETC Group has also highlighted concerns over the key role of biomass as a base for synthetic biology industrial processes, as discussed above in section 5.1 (ETC 2013b). Related to this, ETC Group questions whether a switch from monoculture oil palm plantations to monoculture sugar plantations (for feedstock for synthetic biology processes) is an improvement for biodiversity (ETC 2013a).

5.6. Applications for chemical production

A significant potential use of synthetic biology is the engineering of plants and microbes to produce raw materials that are currently produced using synthetic chemistry (Garfinkel and Friedman 2010; Philp *et al*. 2013). For example, some bioplastics, such as polylactic acid plastics, use synthetic biology techniques and are made from biomass such as sugar cane instead of petroleum (Philp *et al*. 2013). DuPont produces bio-based 1,3 propanediol by fermenting corn sugar with a "patented micro-organism" that converts glucose to propanediol.[46] Consolidated bioprocessing (CBP) aims to engineer what would be several processing steps into the functions of one microorganism, resulting in cost savings (Philp *et al*. 2013; Garfinkel and Friedman 2010). Synthetic biology is also being explored for new industrial processes, such as research into harvesting reserves of hydrocarbons with microbial digestion (PCSBI 2010).

Industry and civil society have predicted positive and negative impacts on biodiversity from the application of synthetic biology to produce chemicals. Such products and processes may result in decreased use of non-renewable resources and "less impactful manufacturing processes in general" (Garfinkel and Friedman 2010). Civil society groups have expressed concern that, as synthetic biology companies shift their focus from biofuels to the smaller but more lucrative markets of chemicals, the "same polluting companies" are taking the lead in developing bioplastics (ETC 2010; ICSWGSB 2011). The ETC Group questions whether the use of synthetic biology is leading to "greener" products or industrial processes. They point to the use of synthetic biology and biomass to produce products with similar problems as the non-synthetic biology versions, such as bio-based PVC (which still requires chlorine in its production) and many bio-plastics (some of which cannot compost, or would do so only in industrial composters) (ETC 2010). In a review article, König *et al*. (2013) note that some methods of producing biodegradable plastics may have more environmental impacts such as the release of carcinogens and eutrophication than fossil-based polymers.

6. GENERAL BIOSAFETY CONCERNS

This section focuses on biosafety concerns related to the accidental or intentional release of organisms resulting from synthetic biology techniques that are applicable to all types of applications seen in section 5 above. These include concerns related to ecosystem-level impacts, gene flow, and the emergence of unpredictable properties.

6.1. Ecosystem-level impacts

Unintentional or intentional release of organisms resulting from synthetic biology techniques to ecosystems outside of a contained laboratory or production facility could negatively impact biodiversity. One set of concerns center on the possibility of such organisms' survival and persistence. For example, organisms resulting from synthetic biology techniques could displace existing species because of fitness advantages (intentional or otherwise) and become invasive (Redford *et al*. 2013; Snow and Smith 2012; Wright *et al*. 2013). The International Civil Society Working Group on Synthetic Biology (ICSWGSB 2011) expresses concern that organisms resulting from synthetic biology techniques could

46 *See: http://www2.dupont.com/Renewably_Sourced_Materials/en_US/proc-buildingblocks.html, accessed on 23 Feb. 2014. The ICSWGSB (2011) identifies this process as using synthetic biology techniques. Esvelt & Wang identify DuPont's work on propanediol as a "great example of genome-level metabolic engineering" (2013).*

Source: Macroscopic Solutions, LLC

become a new class of pollutants if they persist, for example algae that continues to produce oils or organisms engineered to break down sugarcane degrading sugar in the local environment. Even if the organisms did not persist for long periods, they could disrupt ecosystems and habitats, for example, if algae engineered for biofuel production escaped containment and bloomed (Redford *et al*. 2013; Snow and Smith 2012; Wright *et al*. 2013).

Notwithstanding that risk assessments must be carried out on a case-by-case basis, there is disagreement within the scientific and policy communities over the degree and probability of harm that organisms resulting from synthetic biology techniques that are intended for contained use could cause if released (RAE 2009; Lorenzo 2010; Snow 2011; Zhang *et al*. 2011; Dana *et al*. 2012; Snow & Smith 2012; Tait & Castle 2012). A common argument is that an accidental release of organisms resulting from synthetic biology that are intended for contained use would likely not lead to survival and propagation because engineered changes generally lead to reduced fitness (Garfinkel and Friedman 2010; Lorenzo 2010; RAE 2009; Moe-Behrens *et al*. 2013). On the other hand, the limit of detection for relevant microbes may be too high (i.e. a large population of microbes is needed in order to be detectable) to extrapolate their extinction, and microorganisms that have been released into an environment may have long lag times before they develop into a population that is large enough to be detected or to cause an ecological change. For example, it was popular for some decades to speculate that the rise of antibiotic resistance in medically relevant bacteria would disappear if the associated antibiotics were temporarily withdrawn. This did not turn out to be the case. After resistance levels fell below detection and the drug was reintroduced, resistance emerged unexpectedly rapidly. Assumptions that resistance rendered these bacteria less fit in the absence of the antibiotic also turned out to be frequently incorrect (Heinemann *et al*. 2000). Snow (2011) and Snow and Smith (2012) point out that (i) the majority of research in synthetic biology uses microbes as hosts, (ii) microbes have a particularly high potential for rapid evolutionary change, and (iii) modified microbes resulting from synthetic biology techniques that seem innocuous or weak might survive due to mutations. Ecologists and commentators urging caution point out that organisms resulting from synthetic biology techniques cannot be retrieved once released (Dana *et al*. 2012; Snow and Smith 2012; FOE *et al*. 2012). Wright *et al*. (2013) note that even genetically modified microorganisms that may be programmed to "self-destruct" pose an environmental risk, as their DNA can potentially be scavenged by other organisms after they have died (see section 6.2 below).

Some anticipated future applications of synthetic biology would require the intentional release of organisms resulting from synthetic biology techniques into the environment (Anderson *et al*. 2012), which may present additional complexities and types of potential negative impacts. Many synthetic biologists are aiming to design microorganisms that are sufficiently hardy for release into the environment (section 5.2). Belgium's Biosafety and Biotechnology Unit notes that "risk assessors and regulators have relatively little experience considering the potential risks [sic] posed by the intentional release of micro-organisms," and that environmental microbiology is more complex that of higher organisms (Pauwels *et al*. 2012). They go on to say that it is still "premature" to address potential challenges since they consider environmental applications of synthetic biology to still be several years away (Pauwels *et al*. 2012). Marris and Jefferson (2013) also note that regulatory agencies in the United States, Europe and elsewhere, which have been conducting risk assessment for crops resulting from modern biotechnology, have very little experience of risk assessment for genetically modified micro-organisms. Rodemeyer, writing for the WWICS Synthetic Biology Project, further notes that regulatory agencies have had "relatively little experience considering the potential risks [sic] posed by the eventual evolution of genetically engineered microorganisms intended for non-contained use"; most GMOs/LMOs that have been intentionally introduced into the environment are annual food crops, therefore, evolution has not been seen as a relevant risk factor (Rodemeyer 2009). Risk assessment of microorganisms resulting from modern biotechnology is among the topics identified by a group of experts established by the Parties to the Cartagena Protocol on Biosafety for the development of guidance (CBD 2014).

6.2. Gene flow

Altered DNA could be transferred from organisms resulting from synthetic biology techniques to other organisms, either by sexual or horizontal gene flow/transfer. Sexual or "vertical" gene flow occurs when genes from one organism are passed on to populations of the same species or a related species through reproduction (Hill *et al*. 2004). This can occur through pollen exchange, particularly if an engineered crop is in close proximity to wild relatives, as may occur in centers of biodiversity (Rhodes 2010). Gene flow into an ecosystem can also occur via seed dispersal and vegetative

propagation. An example from the past decades of genetically modified crop use is the reported presence of transgenes in landraces of maize (Quist and Chapela 2001; Piñeyro-Nelson *et al*. 2009) and of recombinant proteins in wild populations of cotton in Mexico (Wegier *et al*. 2011).

Genes from organisms resulting from synthetic biology techniques could also transfer to unrelated species through horizontal gene transfer (HGT). HGT is a naturally occurring phenomenon that may happen in three ways: 1) transformation, in which naked DNA is picked up and incorporated by an organism; 2) conjugation, through DNA transfer from one organism to another by plasmid; and 3) transduction, through DNA transfer from one organism to another by virus (Snow and Smith 2012; Hill *et al*. 2004). Much is not understood about HGT, including its frequency and mechanisms of transfer, but recent research has found that HGT plays a role not just in the evolution of bacteria and archaea, but also in the evolution of eukaryotic genomes (Rocha 2013; Schönknecht *et al*. 2013). HGT is common among microbes (Hill *et al*. 2004; Rocha 2013). HGT from symbiotic algae to animals has been observed, in the uptake of an algal nuclear gene by a sea slug to become photosynthetic (Rumpho *et al*. 2008). HGT thus represents a potential mechanism for the transfer of altered genetic material, which is possible even if the original organism produced through synthetic biology has died (Wright *et al*. 2013). Gebhard and Smalla (1999), for example, have shown that DNA from genetically modified sugar beet could persist in soil for two years. The potential for HGT, taking into account the potential persistence of the modified genetic elements in the environment, is an important consideration in the risk assessment of organisms resulting from modern biotechnology and synthetic biology.

The transfer of genetic material from an organism resulting from synthetic biology techniques to another organism may change biodiversity at a genetic level (genotype) and may spread undesirable traits (phenotype). Some scientists, commentators, and civil society groups have expressed concern that the spread of novel DNA may result in undesirable traits in other organisms, such as those encoding antibiotic resistance (commonly used as a marker in synthetic biology and classic genetic engineering) or the production of enzymes that break down cellulose (ICSWGSB 2011; Tucker and Zilinskas 2006; Wright *et al*. 2013). Even if no undesirable phenotypes are detected, the spread of synthetically designed DNA into other species is considered by some to be "genetic pollution" (FOE 2010; ICSWGSB 2011; Marris and Jefferson 2013; Wright *et al*. 2013). There is disagreement whether genetic pollution *in itself* is harmful. Marris and Jefferson (2013) identify synthetic biologists and environmental NGOs as generally assuming that the transfer of genetic material needs to be prevented, while the European regulatory system does not consider the transfer of genetic material as an adverse effect in itself, but a potential mechanism by which adverse effects could occur.

It is also important to note that unpredictable consequences and ecological harms may result from HGT *into* modified organisms. HGT from wild organisms into modified ones may, for example, inactivate biological containment devices or complement engineered auxotrophies, allowing the modified organisms to survive in areas where they are not intended to go (see section 7.2).

6.3. Emergence of unpredictable properties

The scientific community speculates that synthetic biology could result in radically different forms of life, with "unpredictable and emergent properties" (RAE 2009; Garfinkel and Friedman 2010; Mukunda *et al*. 2009). However, there is no agreement over the significance of such unexpected possibilities. Pauwels *et al*. (2013) explain that, even if the sources of genetic sequences are known and understood, it may be difficult to assess how all of the new circuits or parts will interact or to predict the possibility of unexpected emergent properties. Similarly, Schmidt and de Lorenzo (2012) explain that: "It is paradoxical that such an impressive ability to synthesize DNA does not match our much more limited knowledge to forward-engineer genetic devices with more than 20 genes or biological parts. This places the synthetic biology field in a territory where designing new-to-nature properties will still rely for some time on trial-and-error approaches where emergence of unexpected, perhaps undesirable traits might certainly occur". Dana *et al*. (2012) reflect a concern that "no one yet understands the risks that synthetic organisms pose to the environment, what kinds of information are needed to support rigorous assessments, or who should collect such data".

In discussions of the danger of unforeseen results in synthetic biology, a common example is an experiment in 2000 using classic genetic engineering technology. An engineered mousepox intended to induce infertility was unexpectedly virulent, killing all of the unvaccinated mice and half of the vaccinated mice (Jackson *et al*. 2001, cited or described in: Douglas and Savulescu 2010;

Garrett 2011; Mukunda *et al*. 2009; Schmidt & de Lorenzo 2012; Wilson 2013). Some scientists question how "unexpected" the increased virulence was (Müllbacher & Lobigs 2001) (although the researchers who inadvertently developed a lethal mouse virus continue to insist that, even if increased virulence could have been predicted, it was still surprising that immunized mice were susceptible to the virus (Selgelid & Weir 2010)). Although not a result of synthetic biology techniques, the mousepox case is raised in the context of synthetic biology as an example of the potential for producing more pathogenic products (Douglas & Savulescu 2010; Schmidt & de Lorenzo 2012; Wilson 2013) and the possible limits of predictive knowledge (Garrett 2011; Mukunda *et al*. 2009). One commentator noted about the mousepox case: "While the problem of unforeseen results is not unique to synthetic genomics, the combining of multiple sources of DNA sequence (not just, say, a bacterial vector and a specific gene as is exemplified by standard recombinant DNA techniques), particularly when this can occur very rapidly, may be of some concern" (Fleming 2006).

7. STRATEGIES FOR CONTAINMENT

Containment strategies to prevent the unintentional release of organisms resulting from synthetic biology techniques and/or exposing the environment to such organisms may be physical (e.g. physical barriers) or biological (e.g. inhibited ability to reproduce or survive outside of contained system) (Schmidt and Lorenzo 2012). Both physical and biological containment strategies are being explored as means to reduce the risks and potential negative impacts of organisms resulting from synthetic biology techniques.

7.1. Physical containment

The UK Healthy and Safety Laboratory noted that research and production of organisms resulting from synthetic biology under contained use conditions could be used to develop evidence on how to regulate future applications that may involve intentional release, in a step-by-step approach (Bailey *et al*. 2012). Future uses of synthetic biology may straddle the line between containment and release. For example, French *et al*. (2011) consider their prospective arsenic biosensor that may be used in a contained device - but outside of a laboratory - as raising less concerns than biosensors that are designed for direct introduction into the environment. Moreover, the level of containment of organisms developed through synthetic biology will also influence the likelihood of their accidental environmental release. For example, because of their need for exposure to sunlight and carbon dioxide (WWICS 2013), algae that are grown in open ponds may be more prone to accidental release than organisms contained in laboratory facilities.

It is widely acknowledged among microbial biologists and ecologists that physical containment is never fail-proof (Moe-Behrens *et al*. 2013; Schmidt and Lorenzo 2012; Snow 2010; Wright *et al*. 2013; Marris and Jefferson 2013). One of the conclusions that Schmidt and de Lorenzo (2012) draw from decades of research and use of recombinant DNA is that "it is naïve to think that engineered organisms have never escaped the laboratory. They often have, and massively". Synthetic biologists Wright *et al*. (2013) call it prudent to include some form of physical containment, but caution that "failure in [the physical containment] is a matter of when, not if". The disagreement is thus largely not about whether engineered organisms will escape physical containment, but rather over the degree of concern this should elicit and the appropriate responses.

There is significant disagreement over how stringent physical containment measures should be for synthetic biology, stemming from disagreement over the seriousness of the threats posed by organisms resulting from synthetic biology techniques (EGE 2009; FOE *et al*. 2012; Garfinkel *et al*. 2007, Marlière 2009). Requiring synthetic biology research to take place only in BSL 3 or 4 laboratories would significantly restrict synthetic biology research to a few laboratories (Garfinkel *et al*. 2007). *Principles for the Oversight of Synthetic Biology*, collaboratively drafted by civil society groups and endorsed by 111 organizations, calls for the strictest levels of containment of synthetic biology (FOE *et al*. 2012). They do not specify a specific Biosafety Level, but more generally call for physical, geographical and biological confinement strategies that prevent the release of organisms resulting from synthetic biology techniques into the biosphere (Ibid.). Tucker and Zilinskas, experts in nonproliferation policy, declared "it would be prudent to [...] treat synthetic microorganisms as dangerous until proven harmless. According to this approach, all organisms containing assemblies of BioBricks would have to be studied under a high level of biocontainment (Biosafety Level, BSL, 3 or even 4) until their safety could be demonstrated in a definitive manner" (Tucker and Zilinskas 2006). On

the other hand, the US Presidential Commission for the Study of Bioethical Issues (PCSBI 2010) found that the *NIH Guidelines*' existing guidance on the BSL for any specific experimental agents and designs were adequate for synthetic biology at its current stage of development. The Center for Genetics and Society published an open letter signed by 58 civil society groups who consider that the "Commission's recommendations fall short of what is necessary to protect the environment, workers' health, public health".[47]

The Cartagena Protocol on Biosafety, in article 3(b), defines contained use as "any operation, undertaken within a facility, installation or other physical structure, which involves living modified organisms that are controlled by specific measures that effectively limit their contact with, and their impact on, the external environment". The Cartagena Protocol does not elaborate on how these measures are to be implemented but, at their seventh meeting, the Parties to the Protocol will deliberate on the development of tools and guidance to facilitate the implementation of the Protocol's provisions on contained use of LMOs.[48]

7.2. Biological containment

In reference to the need for containment, researchers sometimes note that engineered organisms generally have reduced fitness, referencing past experience with genetically modified micro-organisms (Bassler 2010; WWICS 2011; de Lorenzo 2010). However, some synthetic biologists see synthetic biology as providing tools that could result in hardier organisms, and lack of fitness does not discount the possibility of the transfer of genetic material to other organisms. Therefore, among synthetic biologists and in policy discussions, a commonly suggested response to the limitations of physical containment and the possibility of organisms successfully designed for environmental release is that synthetic biology be used to design organisms with "built-in safety features" (RAE 2009; Marlière 2009; Moe-Behrens *et al*. 2013; PCSBI 2010; Wright *et al*. 2013). In 2009, synthetic biologist Philippe Marlière argued that most experts see physical containment as "a futile tribute to superstition", and that biological containment was the "surest if not simplest way to avoid risks of dissemination and contamination" (Marlière 2009). There are four general areas of research that aim to develop built-in biological containment: induced lethality; horizontal gene transfer prevention; trophic containment; and semantic containment.

The idea of engineered induced lethality (also referred to as "kill switch" or "suicide gene") is frequently raised as a solution to the problem of survival and persistence (PCSBI 2010; Venter 2010), but there are significant constraints to its effectiveness. The US Presidential Commission for the Study of Bioethical Issues (PCSBI) frequently mentioned "suicide genes or other types of self-destruction triggers" as a way to reap the benefits of synthetic biology while avoiding potential harms (PCSBI 2010). This is also a popular suggestion among iGEM teams as a way to respond to biosafety concerns (Guan *et al*. 2013). However, as recently discussed by Wright *et al*. (2013), Schmidt and de Lorenzo (2012), and Moe-Behrens *et al*. (2013), kill switches in microbes are prone to failure. The selective pressure acting to inactivate or lose suicide genes (i.e. through mutation) is expected to be stronger than for other genes, precisely because the suicide genes are expressly designed to kill the host cell. Moreover, while suicide genes are intended to be active only under certain conditions, there may be varying amounts of "leaky" expression, which means that the selective pressure is present even under normal conditions where the host cells are intended to thrive. Wright *et al*. (2013) corroborate this notion by writing that "dependency devices based solely on toxins seem designed for failure due to their inability to withstand mutation over time".

Trophic containment is another suggested biological barrier where auxotrophic organisms are designed to be unable to synthesize a compound that is required for its survival and that cannot be found outside a controlled environment (Marlière 2009; Moe-Behrens *et al*. 2013; PCSBI 2010; Wright *et al*. 2013). Once auxotrophic microbes escape, they die without the necessary compound. There are some drawbacks to auxotrophic containment. The compound required for survival might be available in the environment to which it escapes (Moe-Behrens *et al*. 2013). Even if the compound is not present in the environment, organisms may parasitically rely on metabolites from other organisms, or gene transfer could revert the containment by introducing the necessary gene (Moe-Behrens *et al*. 2013; Wright *et al*. 2013). Moe-Behrens *et al*. note that only a few of the genetic safeguard approaches, including engineered auxotrophy, have met the recommended limit of engineered microbe survival of less than 1000 cells per 2 litres (Moe-Behrens *et al*. 2013). A related method of containment that is being explored in influenza research involves modifying the influenza virus to express specific micro-RNA target sites. This was found to attenuate influenza pathogenicity in

47 Available at http://www.geneticsandsociety.org/article.php?id=5517.

48 Document UNEP/CBD/BS/COP-MOP/7/15 on "Contained use of living modified organisms" is available at http://bch.cbd.int/protocol/meetings/documents.shtml?eventid=5193.

different species that express the specific micro-RNA (Langlois *et al*. 2013). It is hoped that a similar approach could add extra precaution when studying other pathogens (Devitt 2013).

Another containment strategy is preventing horizontal gene transfer (HGT); this is also still in development. Scientists from UC Berkeley's Department of Bioengineering suggest that synthetic biology organisms could eventually be engineered to prevent HGT, through strategies such as deleting certain plasmid sequences, producing phage-resistant strains, and mutating specific genes in order to prevent the uptake of DNA from the environment (Skerker *et al*. 2009). Skerker *et al*. (2009) express confidence that HGT can be understood sufficiently enough to be prevented. Other synthetic biologists acknowledge that minimizing the uptake of 'free' DNA via transformation (as opposed to conjugation or transduction) continues to be challenging (Wright *et al*. 2013). Ecologists and social scientists identify HGT as a key area for risk research (Dana *et al*. 2012; Snow and Smith 2012).

Semantic containment would require creating organisms that "cannot communicate with the extant biochemistry of the existing live world" (Schmidt and Lorenzo 2012). Xenobiology is the main area of research exploring the creation of orthogonal biological systems. By introducing unnaturally occurring nucleotides or an alternate backbone besides ribose or deoxyribose into the nucleic acid of micro-organisms, a cellular information system that retains the original functions but cannot be read by naturally occurring enzymes (Marlière 2009; Schmidt and Lorenzo 2012; Wright *et al*. 2013). Orthogonal systems based on xenobiology "offer significant hope for microbial cells designed to have minimal genetic interaction with nature" (Wright *et al*. 2013), but synthetic biologists acknowledge that they are years (possibly decades) away from achieving truly orthogonal organisms resulting from synthetic biology techniques, l*et al*one demonstration of containment (Moe-Behrens *et al*. 2013; Wright *et al*. 2013). Furthermore, xenobiology organisms' effects on natural organisms are unclear. Recent research suggests that alternative backbone nucleic acids can bind with natural DNA and RNA, with toxic effects (Moe-Behrens *et al*. 2013; Sutherland *et al*. 2013).

According to Wright *et al*. (2013), "The current consensus in the synthetic biology research community is that multiple biosafety mechanisms will be needed to ensure system redundancy in case of component inactivation". The same authors also note that the higher the complexity, the more prone it may be to failure; thus, safety components must be chosen carefully.

Civil society groups, conservation biologists, and social scientists have urged that biological containment strategies based on synthetic biology not be relied upon as biosafety measures until thorough risk assessments have been carried out (King 2010; FOE *et al*. 2012; Snow 2010; Sutherland *et al*. 2013). The 111 organizations endorsing *Principles for Oversight of Synthetic Biology* called for the restriction of xenobiology research within laboratories (FOE *et al*. 2012). The ICSWGSB calls on the CBD COP to recommend that Parties not approve biocontainment strategies based on synthetic biology "for field testing until appropriate scientific data can justify such testing, and for commercial use until appropriate, authorized and strictly controlled scientific assessments with regard to, *inter alia*, their ecological and socio-economic impacts and any adverse effects for biological diversity, food security and human health have been carried out in a transparent manner and the conditions for their safe and beneficial use validated" (ICSWGSB 2011). These groups are responding to what they perceive as overly optimistic expectations of many synthetic biology commentators for the promise of built-in biosafety.

7.3. Social aspects of containment

Because containment strategies occur within social and institutional systems, the effectiveness and types of containment depend on the conditions of use and characteristics of the users of synthetic biology technologies (Marris and Jefferson 2013). As noted in comments made by one Party on an earlier draft of this document, this requires dialogue between synthetic biologists, regulators, and social scientists.

As a converging field, synthetic biology has attracted people from outside of the life sciences. While this is generally seen as a positive trend, it also represents potential challenges for containment. Many newcomers to the biology laboratories have potentially not had formal biosafety training, and therefore may not know or be able to follow proper protocols for human and environmental safety (Schmidt 2009; NSABB 2010). Professionals attracted to synthetic biology, such as chemists, physicists, engineers, and computer scientists, "may not have been sensitized to the ethical, social and legal norms of the traditional life sciences research communities" (NSABB 2010). Others are early in

Source: Macroscopic Solutions, LLC

their careers in laboratories. For example, the annual iGEM competitions involve college and high school students in synthetic biology experiments (Guan *et al*. 2013).[49]

Some experiments in synthetic biology are carried out by amateur biologists, sometimes referred to as "bio-hackers", or the do-it-yourself biology (DIYbio) community (Ledford 2010; Schmidt 2009; Guan *et al*. 2013). There is contention over how many people are engaging in modern biotechnology outside of formal laboratories and the sophistication of the research and synthesis they are able to do (Bennett *et al*. 2009). Some civil society groups have expressed concerns that such independent researchers have neither the knowledge nor the tools to properly dispose of wastes or prevent release into the environment and have urged that DIYbio and bio-hackers be individually licensed in addition to their laboratories being licensed (EcoNexus 2011; FOE 2010).

Beyond the matter of laboratory safety practices, there is a broader concern that synthetic biology practitioners lack an understanding of ecosystem and biodiversity science. At the US PCSBI hearings, the President of the Hastings Center, Tom Murray, stated:

> "As the relative participation of biologists, familiar with the complexities and the non-linearities of biological systems diminishes, so may an appreciation of consequences of intentional or unintentional perturbations of, for example, eco systems. It is just not the way they think about it. Biologists are trained or at least particularly whole organism biologists even microbial biologists do think about whole organisms and think about environments and ecosystems. That is less true about some molecular biologists, and probably less true about some of the other people that are now coming into synthetic biology…. Why is this important? We need to make sure the people who are on the leading edge of synthetic biology understand the complexities of the systems they will eventually purport to tinker with" (Murray 2010).

8. ADEQUACY OF CURRENT METHODOLOGIES FOR ENVIRONMENTAL RISK ASSESSMENT

Perspectives on the adequacy of environmental risk assessments and regulatory structures designed for GMOs/LMOs resulting from classic genetic engineering in addressing organisms resulting from synthetic biology will depend, in part, on the perceived novelty of synthetic biology. Writing for the WWICS Synthetic Biology Project, Michael Rodemeyer noted that near-term products "derived from well-understood bacterial hosts and natural genetic sequences" and intended for contained use are "likely comparable in risk to currently produced genetically engineered organisms" (Rodemeyer 2009). Similarly, national government reports - such as the US Presidential Commission on the Study of Bioethical Issues (PCSBI 2010), the Belgian Biosafety and Biotechnology Unit (Pauwels *et al*. 2012), and the UK Health and Safety Laboratory (Bailey *et al*. 2012) and UK Synthetic Biology Roadmap Coordination Group (UKSBRCG 2012) - express the view that their regulatory regimes and risk assessment methodologies for genetically modified organisms sufficiently apply to the current and near-term results of synthetic biology techniques. Most of these documents also, however, stress that regulators need to continue to monitor developments in the field, implying that changes may be necessary depending on how synthetic biology develops (Bailey *et al*. 2012; Pauwels *et al*. 2012; UKSBRCG 2012). Rodemeyer (2009), for example, notes that risk assessment will be challenged as the complexity of organisms increases as novel gene sequences are more significantly modified, and as genetic components are assembled from a greater variety of sources. From the perspective of the ICSWGSB (2011), current developments of synthetic biology techniques already demand new risk assessment procedures and regulatory responses. The ICSWGSB (2011) argue that, as current risk assessment methodologies have a strong element of comparison with the risks posed by the recipient or parental organism,[50] they are inadequate for organisms produced using synthetic biology techniques that have no analog in the natural world.

49 iGEM notes that the teams work in BSL1 or BSL2 laboratory spaces at high schools, universities, or similar institutions. The teams are required to follow all applicable laws and university biosafety rules.

50 Among the general principles for risk assessment, Annex III of the Cartagena Protocol on Biosafety states that "risks associated with living modified organisms [...] should be considered in the context of the risks posed by the non-modified recipients or parental organisms in the likely potential receiving environment."

Source: Macroscopic Solutions, LLC

There is also disagreement over the amount of resources that should be channeled to the research of the risks of organisms resulting from synthetic biology techniques. Some researchers reflect concern for the "unknown unknowns" of synthetic biology in their call for significantly increased funding for dedicated synthetic biology risk research. They argue that no one yet understands the risks that synthetic organisms pose to the environment, what kind of information is needed to support rigorous assessments, or who should collect such data. For example, Dana *et al*. (2012), writing as employees of the Synthetic Biology Project at the Woodrow Wilson International Center for Scholars (WWICS) and Ohio State University, argued for a minimal investment of $20-30 million in synthetic biology environmental risk research over the next 10 years to address areas such as: the difference in physiology of naturally occurring organisms and organisms resulting from synthetic biology techniques; how microbes could alter habitats, food webs and biodiversity; the rate of evolution of organisms resulting from synthetic biology techniques; and understanding processes of gene transfer. Tait and Castle (2012), writing from the UK ESRC Innovation Centre, responded that the investment proposed by Dana *et al*. was not yet justified. Tait and Castle (2012) also noted that "the questions raised by Dana *et al*. should be considered as part of any risk-governance system for synthetic biology". Their disagreement thus seems to be around the scale of dedicated risk research, and not the content. Synthetic biologist de Lorenzo (2010b) argues that the results of current synthetic biology research, as well as organisms and commercial products resulting from current synthetic biology applications (i.e., not yet orthogonal systems such as xenobiology) are sufficiently familiar, and that the risk assessments conducted on a case-by-case basis for GMOs/LMOs produced through classic genetic engineering are still appropriate.

Social scientists Zhang *et al*. (2011) recommend recognition of the full range of scientific uncertainties relating to synthetic biology. Drawing on the work of Brian Wynne (1992) and Andy Stirling (2008; 2010), Zhang *et al*. (2011) note that risks describe situations in which possible kinds of damage and their probabilities can be known. Other kinds of limited scientific certainty can be described as uncertainty (when the types of harm can be identified, but not their probabilities), ambiguity (where the measurement or meanings of the kinds of harm are contested), and ignorance (where neither the outcomes nor probabilities can be characterized) (Wynne 1992; Stirling 2010). Zhang *et al*. (2011) warn that, as with other emerging technologies, there has been a tendency among governments to respond to synthetic biology as if it represents only identifiable and measurable risks.

Most existing biosafety regulations, including the Cartagena Protocol on Biosafety, rely on case-by-case assessments of environmental risks which take into account any environment which may be exposed to the organism, the characteristics of the organism and its intended uses. Current and near-term commercial applications of synthetic biology build on techniques of modern biotechnology to create organisms with novel combinations of genetic material. As such, the general risk assessment methodology for living modified organisms is expected to be applicable to organisms produced through synthetic biology, albeit specific considerations will likely be needed to identify any gaps that may exist in the methodologies that are currently in place to assess the environmental risks of living modified organisms and propose guidance on how to fill such gaps. The need for developing risk assessment guidance that focuses specifically on organisms developed using synthetic biology techniques was already foreseen by a group of experts representing the Parties to the Cartagena Protocol on Biosafety (CBD 2014).

A revised risk assessment methodology may not necessarily demand the set-up of regulatory regimes distinct from existing biosafety regimes covering GMOs/LMOs. If and when future commercial applications of synthetic biology evolve to use techniques that do not rely on the *in vitro* manipulation of nucleic acids to cause inheritable changes in an organism, current methodologies for environmental risk assessment may no longer be suitable as these organisms would no longer fall within the scope of many biosafety instruments.

For a more in-depth analysis of the gaps and overlaps with the applicable provisions of the Convention on Biological Diversity, its Protocols, and other applicable international instruments see document UNEP/CBD/COP/12/INF/12.[51]

51 Available at http://www.cbd.int/doc/?meeting=COP-12.

Source: Macroscopic Solutions, LLC

Source: PNNL

Table 1.	Examples of potential positive and negative impacts of synthetic biology applications on conservation and sustainable use of biodiversity
Specific area of application	**Potential positive and negative impacts* on conservation and sustainable use of biodiversity**
Bioenergy applications of synthetic biology	At a significant scale, these approaches could reduce global dependence on fossil fuels and cut harmful emissions (PCSBI 2010) Synthetic biology tools may be used in designing "next generation" biofuels that, it is hoped, will overcome challenges of "first generation" biofuels made from food crops (Webb & Coates 2012) Use of biomass as feedstock in synthetic biology processes may be an environmentally beneficial shift from non-renewable resources (Erickson *et al*. 2011; Georgianna & Mayfield 2012)
	Synthetic biology bioenergy applications could lead to increased extraction of biomass from agricultural land, which may decrease soil fertility (ICSWGSB 2011; Fixen 2007) Increased demand for biomass may lead to displacement of local sustainable uses and environmental harm in tropical and sub-tropical communities (ETC 2010; FOE *et al*. 2012; FOE 2010) If synthetic biology techniques open up new sources of energy such as algae and seaweed, increased demand may encroach on traditional uses (ETC 2013)
Environmental applications of synthetic biology	Micro-organisms resulting from synthetic biology techniques may work as biosensors, helping to identify areas contaminated with specific pollutants (French *et al*. 2011)
	Microbes that are intended for release into the environment could have adverse effects due to their potential for survival, persistence and transfer of genetic material to other micro-organisms
Applications to alter wildlife populations	Synthetic biology techniques might help to identify and treat wildlife diseases (Allendorf *et al*. 2010) Synthetic biology techniques may be used to restore extinct species ("de-extinction"), restoring ecological richness (Church 2013; Redford *et al*. 2013) De-extinction may provide a new paradigm for biodiversity advocacy, based on hope instead of crisis (Brand 2013; Redford 2013) RNA-guided gene drives could potentially prevent the spread of disease, and control damaging invasive species (Esvelt *et al*. 2014) Synthetic biology techniques may be used to target threats to wildlife, such as the spread of diseases borne by insect vectors (Weber and Fussenegger 2012; Esvelt *et al*. 2014)
	Proposed synthetic biology solutions might divert funds and other resources from other conservation efforts (Ehrenfeld 2013; Ehrlich 2013). Proposed synthetic biology solutions might move policy-makers away from addressing underlying causes for biodiversity loss (Redford *et al*. 2013) 'Moral hazard" may reduce society's willingness to support measures to conserve endangered species (Redford *et al*. 2013) Synthetic biology capability may lead to decreased support for *in situ* conservation with impacts on support for existing protected areas (Redford *et al*. 2013) Potential undesired consequences could result from the use of "gene drive" systems to spread traits aimed at the suppression or extirpation of populations of disease vectors (eg. mosquitoes). One such undesired consequence could be the introduction of new diseases through the replacement of the population of the original disease vector by another vector species ("niche substitution") Near-certain spread across political borders, i.e. unintentional or unauthorized transboundary movements, of mosquitoes and other insects used to control diseases (Esvelt *et al*. 2014)

Source: Macroscopic Solutions, LLC

Table 1 continued.	Examples of potential positive and negative impacts of synthetic biology applications on conservation and sustainable use of biodiversity
Specific area of application	**Potential positive and negative impacts* on conservation and sustainable use of biodiversity**
Agricultural applications of synthetic biology	The potential for organisms resulting from synthetic biology techniques in the agricultural production sectors might foster "sustainable intensification" and "land sparing" to reduce land conversion and increase protection of wild habitats (Redford *et al*. 2013) Reduced use of chemical pesticides and fertilizers could have positive ecological impacts (PCSBI 2010). RNA-guided gene drives could potentially support agriculture by reversing pesticide and herbicide resistance in insects and weeds (Esvelt *et al*. 2014). Industrial uses created by synthetic biology might drive significant land use change towards feedstock production (could be a beneficial or negative impact) (Redford *et al*. 2013)
	Possible toxic and other negative effects on non-target organisms such as soil micro-organisms, beneficial insects, other animals and plants; Potential negative impacts to the conservation and sustainable use of biodiversity could arise from the transfer of genetic material to wild populations via vertical gene transfer and introgression
Applications of synthetic biology to replace natural materials	Molecules produced through synthetic biology could enable conservation of plants and animals currently unsustainably harvested from the wild or through unsustainable cultivation (BIO 2012)
	Synthetic biology products could displace products that are key to in-situ conservation projects (ETC 2013a)
Applications of synthetic biology to replace materials made with synthetic chemistry	Synthetic biology alternatives for chemical products and industrial processes may lead to decreased use of non-renewable resources and less environmentally harmful manufacturing processes (Garfinkel & Friedman 2010) Transition to sustainable production and consumption (which protects biodiversity) may be promoted (Redford *et al*. 2013)
	Synthetic biology alternatives for chemical products and industrial processes may not actually be "greener," such as current bioplastics (ETC 2010) Industrial uses created by synthetic biology might drive significant land use change towards feedstock production (could be a beneficial or negative impact) (Erickson *et al*. 2011; Redford *et al*. 2013)

* In addition to the specific examples of potential adverse effects listed in this table, general biosafety considerations (section 6) also apply, as appropriate, to the accidental or deliberate release of organisms developed through synthetic biology listed in this table.

Source: Macroscopic Solutions, LLC

Source: Christine Cooper

E. SOCIAL, ECONOMIC AND CULTURAL CONSIDERATIONS ASSOCIATED WITH THE COMPONENTS, ORGANISMS AND PRODUCTS RESULTING FROM SYNTHETIC BIOLOGY TECHNIQUES

This section discusses potential positive and negative impacts of the components, organisms and products resulting from synthetic biology with regard to social, economic and cultural considerations. Table 2 at the end of this section provides examples of potential positive and negative impacts in the context of biosecurity, economic, health, ethical and intellectual property.

9. BIOSECURITY CONSIDERATIONS RELATING TO BIODIVERSITY

A common definition of biosecurity is an effort to "prevent misuse or mishandling of biological agents and organisms with an intent to do harm" (PCSBI 2010). Synthetic biology presents potential challenges to biosecurity, as well as potential tools to aid in security efforts.

Biosecurity concerns related to biodiversity include the use of synthetic biology to create destructive pathogens targeting agriculture or other natural resource bases. Existing livestock and crop diseases could be made more lethal, and novel pathogens designed to impact agricultural biodiversity (Kaebnick 2009).[52] Mukunda *et al*., writing from MIT and Boston University, predict that biological weapons customized to attack specific groups are highly likely in the long term (10 or more years) (Mukunda *et al*. 2009).

There is heated debate as to the level of threat of biological weapons, but broad consensus that advances in biotechnology are likely to increase the dangers posed by biological weapons (Mukunda *et al*. 2009). Mukunda *et al*. (2009) classify potential impacts of synthetic biology on offense as primarily increasing capabilities for acquisition of biological weapons and, in the long term, the effects of such weapons, including enhanced lethality and infectiousness.

Infectious viruses have been created using what some consider as synthetic biology techniques; it is predicted that the creation of bacterial pathogens may be possible. In 2005, researchers at the US Centers for Disease Control and Prevention (CDC) constructed a virus with the complete coding sequences of the eight viral gene segments of the extinct 1918 Spanish influenza virus, following genomic RNA retrieved from autopsy materials and the remains of a victim found buried in the Alaskan permafrost (Tumpey *et al*. 2005). An infectious poliovirus was produced in an American laboratory in 2002, using oligonucleotides ordered from a commercial supplier (Cello *et al*. 2002).[53] Mukunda

52 *Most literature on biosecurity considerations of synthetic biology focuses on human targets, but this analysis applies to biodiversity-associated biosecurity as well.*

53 *These two examples are frequently noted when discussing synthetic biology (see Douglas & Savulescu 2010; Mukunda et al. 2009; RAE 2009). However, one organization commented on an earlier draft of this document that some argue the techniques used in both of these cases are not synthetic biology. Both of these projects involved sequencing parts or all of the target viral genome, and then synthesizing the necessary oligonucleotides (Cello et al. 2002; Tumpey et al. 2005). Tumpey et al. (2005) generated the influenza viruses using a "reverse genetics system." Cello et al. (2002) assembled the poliovirus entirely from oligonucleotides.*

et al. rate the synthesis of viruses as "relatively easy" at present, and thus synthetic biology may be expanding the pool of actors able to acquire agents for biological warfare. In the medium term future, they anticipate the creation of new organisms with novel properties (Mukunda *et al*. 2009). This aligns with the 2007 analysis by Garfinkel *et al*. that synthesizing highly pathogenic viruses will become easier, and that pathogenic bacteria may eventually be possible. At the time, Garfinkel *et al*. (2007) noted that over the next five years, "constructing an infectious virus [would] remain more difficult than obtaining it from nature or from laboratory stocks," but that this could be reversed within 10 years.

Synthetic biology could provide tools for responding to biosecurity risks. The US PCSBI claims it is "easy to anticipate potential benefits" of synthetic biology to biosecurity, such as identifying biological agents of concern and countering biosecurity threats (PCSBI 2010). Synthetic biologist Drew Endy urges that synthetic biology be understood in terms of its "net contribution to risk exposure and not only risk creation" (Endy 2005, Fig. 3). Thus, although synthetic biology can be used to create threats, tools such as DNA synthesis can help identify and respond to biological threats, for example by accelerating the ability to analyze the pathogen and more rapidly synthesize vaccines or vaccine precursors (Endy 2005). Similarly, Mukunda *et al*. point out that synthetic biology could be used for defense, such as improved surveillance to detect pathogenic agents, accelerate vaccine production, and provide therapies for some pathogens (Mukunda *et al*. 2009).

10. ECONOMIC CONSIDERATIONS RELATING TO BIODIVERSITY

The global market for synthetic biology products is growing rapidly, as are investments in synthetic biology research. As seen in section 1, the global synthetic biology market is expected to grow to $11.8 billion in 2018. While smaller than the estimated global market for nanotechnology ($20.1 billion in 2011, $48.9 billion in 2017), synthetic biology's predicted compound annual growth rate of 45.8% outshines nanotechnology's 18.7%.[54] The WWICS Synthetic Biology Project estimates that the US and European governments funded over a half billion USD in synthetic biology research between 2005 and 2010 (WWICS 2010).

There is no clearly agreed definition or scope to the term "bioeconomy"; definitions either focus on the tool of biotechnology or on the use of biomass as a fuel and raw material. The 2009 OECD document *The Bioeconomy to 2030: Designing a Policy Agenda* defines bioeconomy as "a world where biotechnology contributes to a significant share of economic output." (OECD 2009). The United States' White House's *National Bioeconomy Blueprint* similarly defines bioeconomy as "economic activity that is fueled by research and innovation in the biological sciences" (US White House 2012). The European Commission's definition of bioeconomy is broader: "an economy using biological resources from the land and sea, as well as waste, as inputs to food and feed, industrial and energy production. It also covers the use of bio-based processes for sustainable industries" (EC 2012).[55] Civil society groups' definitions of the bioeconomy are similar to that of the European Commission.[56] The Global Forest Coalition describes it as a post-fossil fuel economy, "heavily based on the use of biomass, both as a fuel and as a raw material from which to manufacture a wide range of products, including plastics and chemicals" (Hall 2012). The ETC Group sees the bioeconomy as relying on three inter-related and reinforcing concepts: the biomass economy, moving from fossil and mineral resources to biological raw materials; the biotech economy, in which genetic sequences are the building blocks for designed biological production systems; and the bioservices economy, in which new markets in ecosystem services enable trading of ecological credits (ETC 2010).

States, industry, and civil society identify synthetic biology as playing a potentially significant role in the bioeconomy. The Government of the United States of America names synthetic biology as an emerging technology that "holds vast potential for the bioeconomy, as engineered organisms could dramatically transform modern practices in high-

54 *See http://www.bccresearch.com/report/nanoparticles-biotechnology-drug-development-delivery-bio113a.html. Accessed on 17 April 2013.*

55 *The EC's Strategy describes the bioeconomy as including the sectors of "agriculture, forestry, fisheries, food and pulp and paper production, as well as parts of chemical, biotechnological and energy industries" (EC 2012b).*

56 *For all of these actors, the bioeconomy is a narrower concept than UNEP's "Green Economy" (an economy "that results in improved human well-being and social equity, while significantly reducing environmental risks and ecological scarcities") (UNEP 2011).*

Source: Macroscopic Solutions, LLC

impact fields such as agriculture, manufacturing, energy generation, and medicine" (US White House 2012). Industry analysts see a "bright future" in the bio-based economy for developers of biochemicals, biomaterials, bioactive ingredients, and processing aids (Huttner 2013). The ETC Group describes synthetic biology as a "game-changer," expanding the "commercial possibilities for biomass" (ETC 2010).

State-led policies and strategies are driven by the anticipated benefits of an expanded global bioeconomy. The EC is pursuing the bioeconomy to "reconcil(e) demands for sustainable agriculture and fisheries, food security, and the sustainable use of renewable biological resources for industrial purposes, while ensuring biodiversity and environmental protection" (EC 2012a, 1). The European Commission three-part Action Plan includes: investing in research, innovation and skills; reinforcing policy interaction and stakeholder engagement; and enhancing markets and competitiveness (EC 2012b). The US Obama Administration is prioritizing the bioeconomy "because of its tremendous potential for growth" as well as its potential to "allow Americans to live longer, healthier lives, reduce our dependence on oil, address key environmental challenges, transform manufacturing processes, and increase the productivity and scope of the agricultural sector while growing new jobs and industries" (US White House 2012). Brazil is aligning its strategies to become the "No.1 Global Bioeconomy," building on its natural resources base and extensive biodiversity.[57] And States that have not yet developed bioeconomy-specific strategies are adopting the language of the bioeconomy, such as the Malaysian Minister of Natural Resource and Environment identifying bioeconomy as key to transforming Malaysia into a high-income country.[58]

Engagement by some civil society groups on synthetic biology is significantly motivated by anticipated dangers of an expanded global bioeconomy. Some civil society groups have expressed deep concern over the methods by which a transition from fossil fuels to renewable resources is proposed. As described in section 5.1, a major concern is that the necessary scale of extraction and use of biomass for a global bioeconomy is ecologically unsustainable (Hall 2012; ETC 2011; ICSWGSB 2011; FOE *et al*. 2012). The new bioeconomy also potentially threatens "older "bio-based" economies represented by billions of people with preexisting claims on the land and coastal waters where biomass grows" (ETC 2011). The ETC Group cites the World Health Organization statistic that 3 billion people depend on firewood as the primary source of fuel for heat and cooking, and that 2 billion people rely on animals as the main source of power for agriculture and transport (ETC 2011). Many civil society groups express concern that these biodiversity-based economies depend on the same natural resource as the new bioeconomy, and therefore stand to be displaced by land and resource grabs (ETC 2011; ICSWGSB 2011; Hall 2012).

Many of the first wave synthetic biology commercial applications replicate naturally-occurring molecules that are expensive or difficult to source outside the laboratory or produce in the laboratory using synthetic chemistry (Wellhausen and Mukunda 2009). Product displacement can potentially ease negative pressures on wild or cultivated species, but it can also displace cultivation practices, often in topical and sub-tropical regions.

The anti-malarial semi-synthetic drug artemisinin is a high-profile example of the complicated trade-offs that may result from product substitutions. The artemisinin project of Prof. Jay Keasling of UC Berkeley has been the most popular example of the promise of synthetic biology, and particularly of synthetic metabolic engineering, for the past seven years (Collins 2012; Garfinkel *et al*. 2007; Garfinkel and Friedman 2010; Heinemann and Panke 2006; PCSBI 2010). The shrub *Artemisia annua* has been used in China for centuries to treat a variety of illnesses, including malaria (White 2008). Although announced to the rest of the world in 1979, global politics and issues of price kept artemisinin largely inaccessible. It was not until 2004 that the World Health Organization (WHO) and Global Fund for AIDS, Tuberculosis and Malaria switched to Artemisinic-based Combination Therapy (ACT) (Enserink 2005; Milhous and Weina 2010; White 2008). Since then, the availability - and thus price - of artemisinin has varied wildly, as a combination of bad weather and a glut of new producers has led to year-to-year price swings (Peplow 2013). The Gates

57 *See http://www12.senado.gov.br/internacional/05-18-2012/brazil-can-become-a-leader-in-bioeconomy-says-director-of-national-industry-confederation; http://www.iica.int/Eng/prensa/IICAConexion/IICAConexion2/2012/N13/secundaria4.aspx; and http://www.process-worldwide.com/management/markets_industries/articles/345478/. Accessed on 23 April 2013.*

58 *See http://www.mysinchew.com/node/81046. Accessed on 23 April 2013.*

Source: Macroscopic Solutions, LLC

Foundation gave two grants totaling $53.3 million to the Institute for OneWorld Health to help Prof. Jay Keasling of UC Berkeley engineer the molecular production of artemisinic acid from yeast (Sanders 2013). In 2006, Keasling's group announced their success in engineering the metabolic pathway of yeast using 12 new synthetic genetic sequences to produce high levels of artemisinic acid (Ro *et al*. 2006). OneWorldHealth, Amyris (a commercial synthetic biology company co-founded by Keasling), and pharmaceutical company Sanofi partnered to produce semi-synthetic artemisinin. The term "semi-synthetic" is used because Sanofi has developed a proprietary photochemical method to convert artemisinic acid into artemisinin (Sanders 2013). In 2013, Sanofi announced the launch of large-scale production upon regulatory approval, with plans to produce 35 tons of artemisinin that year and 50 to 60 tons by 2014, the equivalent of 80-150 million ACT treatments (Sanofi and PATH 2013). Thus far, Sanofi has exported approximately 400 kg of semi-synthetic artemisinin to India, the bulk in one shipment worth US$ 350/kg.[59]

There are potential public health benefits from semi-synthetic artemisinin. For seven years, synthetic biology has been described as a cheaper and more efficient way to produce artemisinin than its natural plant source, although a price still has not been named (Garfinkel *et al*. 2007; PCSBI 2010; RAE 2009).[60] Because production of artemisinin is following a "no profit, no loss" model and UC Berkeley included humanitarian use terms in the intellectual property license, it has been expected to be affordable and lead to a "stable cost and steady supply" (Sanders 2013; US PTO 2013). Many analysts anticipate that this will lead to positive public health outcomes (Wellhausen and Mukunda 2009; Peplow 2013). Keasling has also argued that, because individual Artemisia growers sometimes sell to producers of artemisinin monotherapies (which can lead to artemisinin resistance), semi-synthetic production will lead to a more easily controlled market (Thomas 2013).

Semi-synthetic artemisinin may displace cultivation of *Artemisia* by tens of thousands of small-scale farmers. *A. annua* is primarily cultivated on farms in China, Vietnam, East Africa and Madagascar; the average crop area per farmer in China and Africa is around 0.2 hectares (A2S2 2013). Sources within the Artemisinin trade estimate that up 100,000 people (smallholders and wild pickers) depend upon artemisinin for their livelihoods, with a wider social impact when families are factored in to calculation (ETC Group 2013; Charles Giblain[61] 2014 pers. comm.). Initially, semi-synthetic artemisinin was described as a complement to natural cultivation. For example, at the 2013 annual artemisinin conference, the semi-synthetic artemisinin consortium communicated their production was intended to be a complementary source to supplement plant-based artemisinin, that the estimated price would be between US$ 350 and 400, and that the semi-synthetic product would act as a price regulator.[62] But, at an April 2013 conference on synthetic biology and conservation, Keasling noted that "moves are afoot to replace the entire world supply [of artemisinin]". Civil society organizations have long been concerned that this might be an impact of semi-synthetic artemisinin (Thomas 2013; FOE *et al*. 2012). Thomas (2013) noted that "early on, it was not about replacing the agricultural form […] and now I think it is nearly inevitable that it will shift over". The ICSWGSB agrees that malaria drugs must be accessible and affordable, but they question the value of pursuing a high-tech solution over decentralized, sustainable approaches such as supporting expanded smallholder production (ICSWGSB 2011). Moreover, Marris (2013) notes that a crucial issue in the debate between the potential health benefits of artemisinin and the potential loss of income and livelihoods for farmers growing *Artemesia* bushes as a crop is that the hoped-for health benefits for local populations do not simply depend of an increased supply of artemisisin (synthetic or not), but also require a complex set of interrelated political, economic and social conditions.

As noted in several comments on an earlier draft of this document, the displacement of small-scale farmers' crops is not an impact unique to synthetic biology, nor are the experiences of these farmers pre-determined. Indeed, the displacement of natural products by synthetic-biology produced versions follows a "tradition of major technological advances that have displaced former methods of production" (Wellhausen and Mukunda 2009). Wellhausen and Mukunda see semi-synthetic artemisinin and other commercial synthetic biology applications as possibly

59 See: http://www.infodriveindia.com/, accessed 21 Feb. 2014.

60 According to A2S2's tracking of artemisinin imports into India, the average monthly price of artemisinin has been dropping over the past two years, down to US$ 267.51/kg (excl. duty) in December 2013. See: http://www.a2s2.org/market-data/artemisinin-imports-into-india.html, accessed 21 Feb. 2014. Thus far, Sanofi imports of semi-synthetic artemisnin to India have been for more than this.

61 Giblain, CEO of Bionexx in Madagascar, calculated this number based on the Madagascar and Chinese workforces engaged with production and wild picking of Artemisia.

62 See: http://www.a2s2.org/upload/5.ArtemisininConferences/1.2013Kenya/2013ArtemisininConferenceFinalReport.pdf, accessed on 21 Feb. 2014.

improving health and thus the standard of living in developing countries, while simultaneously displacing laborers, exports, and the tax base of those same countries (*Ibid*.). Using the historical examples of natural rubber and indigo dyes' competition with chemically produced alternatives, they explain that sometimes displacement results in impoverishment and sometimes the natural version continues to hold on to some share of the market (*Ibid*.). They see a role for national governments in facilitating industrial restructuring and redistributing any benefits to the "economic losers" (*Ibid*.). The ETC Group has described *Artemisia* growers as the "canaries in the coalmine," providing an early example of the risks that synthetic biology production poses to smallholder producers (ETC 2010). The ETC Group asks what benefits developing countries will experience when the product being displaced is not medicine for a tropical disease. They point to synthetic-biology produced isoprene (rubber), currently in development by Genencor and Goodyear, which could displace smallholders in Asia producing natural rubber (ETC 2007; 2010).

Although artemisinin is a more high-profile example, other synthetic biology versions of natural products are on the near-term horizon. The near-term commercialization of synthetic-biology-produced lauric acids could compete with production from coconut and palm kernel oils (ETC Group 2013). Coconut is a major export crop for the Philippines, primarily from owner-operated farms averaging 2.4 hectares (ETC Group 2013). Palm kernel oil from oil palm primarily comes from large industrial farms in Indonesia and Malaysia. Unilever's investment in Solazyme is related to a desire to move away from the environmentally destructive crop (ETC Group 2013). Tamiflu producer La Roche produces some of its shikimic acid with modified *E. coli*, as opposed to star anise (ETC Group 2013; Rawat *et al*. 2013).

Some are optimistic for developing countries in the global bioeconomy; those who express concern have differing degrees of confidence that harm can be mitigated or avoided. The US PCSBI sees synthetic biology as bringing potential benefits to developing countries, "where health, access to resources, and economic stability are closely linked to one another and to disparities in health and welfare" (PCSBI 2010). The example of artemisinin is frequently put forward as an example of how synthetic biology can significantly improve the health, and thus economies, of developing countries (Ibid.; Garfinkel *et al*. 2007; RAE 2009). A biotechnology-led bioeconomy could also, however, reinforce trends towards the dominance of knowledge-based economies, and the further consolidation of international trade by a few rich states and trans-national corporations (Rhodes 2010). The civil society *Principles for the Oversight of Synthetic Biology* insists that the development of synthetic biology must "not deepen economic and social injustices" through product displacement, increased biomass cultivation and extraction, or the further privatization and control of naturally occurring processes and products (FOE *et al*. 2012). Others recognize the potential that developing countries might fail to benefit from or even be harmed by synthetic biology's role in the global bioeconomy, but see ways that these potential harms can be mitigated. For example, the UK Royal Academy of Engineering recognizes the potential for global inequalities to be "exacerbated" by synthetic biology through product displacement of developing country exports (RAE 2009). Garfinkel and Friedman see many potential synthetic biology applications, such as treating neglected tropical diseases, as potentially most useful to those who can least afford it (Garfinkel and Friedman 2010). But in both cases, these are considered challenges that can be addressed through product-specific arrangements (such as the Gates Foundation's support of artemisinin research and the Sanofi-Aventis no-profit/no-loss model of production) and engagement with the public (Garfinkel and Friedman 2010; RAE 2009).

11. HUMAN HEALTH CONSIDERATIONS RELATING TO BIODIVERSITY

Through the CBD's cross-cutting programme on "health and biodiversity," it is recognized that "we cannot have healthy societies without biodiversity" (CBD 2012). Biodiversity provides sources of medicine, food, clean air and fresh water; loss of biodiversity can negatively impact human health through increased contact with diseases and the loss of substances used as medicines or in medical research (*Ibid*). Synthetic biology may be used for advanced medical interventions but also could have unintended impacts on health and biodiversity.

Classic genetic engineering has been used for over three decades to engineer bacteria to produce molecules such as insulin and vaccines (PCSBI 2010). As with other areas of current and potential future synthetic biology applications, researchers and industries deploying synthetic biology tools are building on the history of established biotechnology, and the lines between "synthetic biology" and classic genetic engineering are not always clear.

Health applications are a major focus of synthetic biology research; much of it is still at the stage of basic research, but some is in commercialization. According to WWICS (2013a), the top application focus of biological systems designers and manufacturers conducting synthetic biology research is medicine. Synthetic biology may provide tools for better understanding disease mechanisms by "rebuilding and studying them in a context isolated from their high degree of natural interconnectivity" (Lienert *et al*. 2014). For example, the oft-cited study synthesizing the 1918 Spanish influenza virus provided insight into the pathogen's virulence factors (Tumpey *et al*. 2005; Weber & Fussenegger 2012). Synthetic biology may be used in drug discovery through developing drug screening platforms (Pauwels *et al*. 2012). One of the expectations for xenobiology is that XNA could be used in diagnostic tests (PCSBI 2010). One focus of synthetic biology research and development is the design of organisms to produce drugs and vaccines. As discussed in more detail in section 4.2.2, semi-synthetic artemisinin for the treatment of malaria is already being produced using metabolic engineering techniques that many consider to be synthetic biology (Sanders 2013). In 2013, researchers at Novartis and Synthetic Genomics published an approach to rapidly generate influenza vaccine viruses, using an enzymatic, cell-free gene assembly technique, producing an accurate vaccine more quickly than previously possible (Dormitzer *et al*. 2013). J. Craig Venter, founder and CEO of Synthetic Genomics, refers to this as "reverse vaccinology" (Industrial Biotechnology 2014). Another approach referred to as "SAVE" (synthetic attenuated virus engineering) (Coleman *et al*. 2008) was used to rationally redesign the genome of an influenza virus, resulting in an attenuated virus with hundreds of nucleotide changes (Mueller *et al*. 2010). Still at the research stage are synthetic biology devices that would provide therapeutic treatment, for example through reprogramming mammalian cells to tackle diseases through prosthetic gene networks, controlling the timed delivery of drugs, more controlled approaches to gene therapy, and engineering micro-organisms to target, penetrate regress tumors (Forbes 2010; Khalil & Collins 2010; Wieland & Fussenegger 2012). In December 2013, two companies using synthetic biology techniques, Intrexon and Agilis Biotherapeutics, LLC, announced a collaboration focused on DNA-therapeutics for Friedreich's ataxia (FRDA), a rare genetic neurodegenerative disease (Intrexon Corp. 2013a). The RAE (2009) anticipates that in the longer term (10 and 25 years) synthetic biology will help to make personalized drugs and highly adaptive vaccines and antibiotics.

It is difficult to anticipate specific negative impacts, but broad categories of potential concerns have been identified related to human health impacts. As discussed earlier, synthetic biology may have negative ecological impacts related to biosafety (section 6), which could then negatively impact human health. Accidental release of organisms resulting from synthetic biology could possibly also have negative impacts on human health (PCSBI 2010; RAE 2009). As was noted by the European Group on Ethics in Science and New Technologies, it is hard to predict the "long-term health-related risks associated with the ecological effects" of synthetic biology (EGE 2009). The coalition of civil society groups that developed *Principles for the Oversight of Synthetic Biology* (FOE *et al*. 2012) as well as the US Presidential Commission for the Study of Bioethical Issues (PCSBI 2010) identify synthetic biology laboratory workers as potentially at risk because of accidental exposure. There is also the possibility that medicines and therapies resulting from synthetic biology techniques may trigger unanticipated adverse effects on human health (König *et al*. 2013; PCSBI 2010). Indirect negative effects to human health could arise if medicines and therapies produced with synthetic biology technologies are inaccessible to some countries because of broad patents and patent "thickets" (see section 13) (König *et al*. 2013).

12. ETHICAL CONSIDERATIONS RELATING TO BIODIVERSITY

Ethical considerations of biodiversity and of how humans relate to biodiversity are recognized as important in the context of the CBD. For example, CBD COP10 established the *Tkarihwaié:ri Code of Ethical Conduct to Ensure Respect for the Cultural and Intellectual Heritage of Indigenous and Local Communities* (Decision X/42). The *Tkarihwaié:ri Code* identifies general ethical principles, including: prior informed consent and/or approval and involvement of ILCs; the fair and equitable sharing of benefits with ILCs; and the precautionary approach, including relevant ILCs and the use of local criteria and indicators in the prediction and assessment of potential harms to biodiversity (Decision X/42, Annex A, Section 2(A)).

Starting as early as 1999, ethicists have actively engaged with the new tools and techniques of synthetic biology (Cho *et al*. 1999). Common considerations have included the ethical debate on whether to ban publications of dual use science discoveries and whether synthetic biologists are

"playing God" (Boldt and Müller 2008; Douglas and Savulescu 2010; Kaebnick 2009; RAE 2009). This section focuses on ethical considerations that relate to biodiversity.

Ethicists disagree whether synthetic biology introduces "new" ethical issues based on the ability to create life rather than modify existing organisms. Ethicists Joachim Boldt and Oliver Müller see synthetic biology as having crossed a threshold from the mere manipulation of life to its "creation" from scratch, thus potentially changing our approach to nature (Boldt and Müller 2008). They are concerned that the ability to design significant portions of organisms may "lead to an overestimation of how well we understand nature's processes and our own needs and interests" (*Ibid*.). Ethicist Christopher Preston invokes Aristotle's distinction between the natural and artifact, arguing that *de novo* organisms, "with no causal chain of viable organisms connecting […] with the historical evolutionary process" should have less value (Preston 2008). A number of commentators counter that such arguments overestimate the current abilities of synthetic biology. Scientists have thus far replicated existing genomes and modified existing cells; this is different from creating a novel organism from scratch (Garfinkel and Friedman 2010; Kaebnick 2009). Social scientists Claire Marris and Nikolas Rose caution against engaging in "speculative ethics" on the assumption that the scientific feat of life-from-scratch is already accomplished (Marris and Rose 2012). Philosopher Beth Preston (2013) argues that synthetic biology presents no new ethical issues; she considers the advent of agriculture as the truly revolutionary moment in human society, and synthetic biology as simply continuing the kinds of human relationships to the natural world established by agriculture. On the other hand, Parens *et al*. (2009) find it important for society to start conversations around the ethics of molding the natural world.

Some areas of synthetic biology research are based on a reductionist view of the world; there is disagreement on the ethical implications of this. Reductionism is the idea that complex entities can be completely explained by the properties of their component parts (Calvert 2008). With the discovery of DNA, the biological sciences took a reductionist turn, attempting to explain life by breaking it down to chemical and physical processes (Cho *et al*. 1999). In recent years, epigenetics has expanded understanding of genes to acknowledge that environmental context has important impacts on gene expression. In some areas of biological sciences, reductionism is seen as a dated and misguided theory that ignores biological complexity. Some synthetic biologists use synthetic biology to try to bypass this complexity, using reductionist logic to design organisms that are less complex (Calvert 2008; EGE 2009). It is an empirical question whether emergence and complexity can be avoided by biological design, but there are also ethical implications of a commitment to reductionism. A reductionist view of life might undermine the special status of living things, if life is seen as "producible, controllable and at our disposal" (Boldt and Müller 2008; Cho *et al*. 1999; ECNH 2010). A similar concern is that synthetic biology moves humanity towards instrumentalism, by which organisms are assigned value based on their instrumental use (EGE 2009). A common counterpoint to these arguments is that life does not necessarily hold such a special status; for example, bacteria are not generally given moral status (ECNH 2010; Douglas and Savulescu 2010). Also, there is not yet evidence that reductionist synthetic biology science has led to a 'slippery slope' of valuing others less (ECNH 2010). Whether an instrumental view of life is problematic depends on how anthropocentric one's ethical stance is (EGE 2009).

Synthetic biology raises ethical issues around harms, benefits and risks. Anderson *et al*. say: "The ability to create synthetic organisms, combined with our inability to control them with solid guarantees, raises the need to consider the ethical implications" (2012). Considerations of biosafety and biosecurity are sometimes discussed as ethical questions of weighing and balancing potential harms and benefits (Boldt and Müller 2008; Cho *et al*. 1999; Douglas and Savulescu 2010; EGE 2009). Some risks might be deemed not morally acceptable because of the severity of harm and/or the probability of harm occurring (Schmidt *et al*. 2009). This raises questions about what level of predictability should be required, and how to weigh possible negative impacts against positive impacts (Anderson *et al*. 2012). The distribution of potential harms and benefits related to synthetic biology products and technologies is also an ethical matter (Schmidt *et al*. 2009; Nuffield 2012; Parens *et al*. 2009). What would be an equitable distribution of synthetic biology related harms and benefits, and how can that distribution be achieved? Ethical issues around harms and benefits also incorporate discussions on global justice, and the potential impacts of synthetic biology on the "technology divide" (EGE 2009).

Questions of synthetic biology's impact on attitudes to biodiversity and conservation are being asked. The US Presidential Commission for the Study of Bioethical Issues (PCSBI) brings up the concern of the "broader effect on how society views and protects biodiversity" (PCSBI 2010). The conveners of a 2013 conference "How will synthetic biology and conservation shape the future of nature?" ask how synthetic biology will change public perceptions of

what is natural, and if it will "challenge the ethical basis for conservation action" (Redford *et al*. 2013). Philosopher Brian Norton speculates that synthetic biology could "encourage an inaccurate model of biodiversity protection as maintaining an inventory of biological units" (Norton 2010). Building on this, Redford *et al*. note the increasing importance of ecosystem services in valuing biodiversity, and ask what will happen if ecosystems with synthesized elements are able to out-compete natural ecosystems, "delivering more services with less biodiversity" (Redford *et al*. 2013). More optimistically, renowned physicist and mathematician Freeman Dyson (2007) imagines a future in which biotech will "give us an explosion of diversity of new living creatures […] Designing genomes will be a personal thing, a new art form as creative as painting or sculpture." Dyson paints this as a largely positive direction for our world, although one with dangers that will need to be managed.

Synthetic biology is seen by some to raise ethical issues related to intellectual property (IP) rights; others consider synthetic biology as a way to avoid ethical challenges to 'patenting life.' Considerations of justice include the distribution of material and non-material goods. The application of intellectual property rights to synthetic biology, such as patents on DNA sequences or organisms resulting from synthetic biology, could restrict the global distribution of products and knowledge (ICSWGSWB 2011; Schmidt *et al*. 2009; ECNH 2010). Civil society groups strongly critique the way that IP regimes have been used in agricultural biotechnology to concentrate power with a few corporations, and they see similar patterns of use occurring in synthetic biology (ETC 2010; FOE 2010; ICSWGSWB 2011) Using synthetic biology to design and synthesize DNA sequences is also, however, seen by some as a way to avoid ethical and legal challenges – particularly those related to patenting the sequence information of naturally occurring DNA (Torrance 2010).

13. INTELLECTUAL PROPERTY CONSIDERATIONS RELATED TO BIODIVERSITY

Intellectual property rights for synthetic biology has been described as a potential "perfect storm"; biotechnology and software already pose serious challenges to the patent system, and synthetic biology's combination of those two areas presents significant challenges (Rai and Boyle 2007). In the field of biotechnology, patents have created an "anti-commons" problem, where broad, ambiguous patent claims restrict the innovation of others (Oye and Wellhausen 2009; Henkel and Maurer 2009; Torrance 2010). Narrow patents, on the other hand, can cause patent "thickets," where complex designs that incorporate many individual parts face an unmanageable number of patents (Rutz 2009; Henkel and Maurer 2009; Rai and Boyle 2007). There is also the possibility that, like with electronics and software, a tipping dynamic will lead to one solution dominating an industry because it is the first to establish common standards (Henkel and Maurer 2007; Henkel and Maurer 2009).

As the field of synthetic biology develops, two main models of intellectual property (IP) for synthetic biology components, organisms, products, and techniques seem to be forming (Calvert 2012). The first heavily relies on patents and is exemplified by the approach of the J. Craig Venter Institute (JCVI) (Gibson *et al*. 2008; Gibson *et al*. 2010; Glass *et al*. 2007). While working at the US National Institutes of Health in the 1980s, J. Craig Venter attracted attention and criticism for leading patent applications of thousands of short DNA sequences (Calvert 2012). In the 1990s, his Institute of Genomic Research (now part of JCVI) sequenced and patented one of the smallest known bacterial genomes, *M. genitalium*. In 2007, scientists at his institute applied for a "minimal bacterial genome" patent (Calvert 2012; Glass *et al*. 2007). This is still pending; NGOs and commentators have expressed concern at its attempted breadth (ETC 2007; ETC 2011; Calvert 2012). The other main model is the BioBrick™ system, modeled on open-source software. On the iGEM's Registry of Standard Biological Parts, contributing researchers post their BioBrick™ parts (DNA-sequences that incorporate standardized sections) on pages accessible to the general public, which allows users to exchange parts and share their experience. Following a similar philosophy of exchange, the BioBricks Foundation has independently developed a BioBrick™ Public Agreement that is essentially a contractual agreement between "Users" and "Contributors" of parts. Contributors may hold patents on the parts, but they promise not to assert any present or future proprietary rights against Users. Unlike open source software, Users have no obligation to openly share the devices or parts they make with the BioBricks™. They can patent novel devices if they want to, meaning that they can build private, proprietary systems on the open platform (Calvert

2012; BioBricks Foundation 2013). As in open-source software, proponents consider this approach as more likely to lead to innovation as well as furthering transparency and openness (Calvert 2012).

IP regimes for synthetic biology could have a variety of impacts on biodiversity and related considerations. In the USA, each patent application costs $10,000 (Henkel and Maurer 2009). If patenting becomes established as the necessary method of claiming of intellectual property rights on synthetic biology, the high cost could influence the kinds of applications of synthetic biology that are pursued (high profit applications targeting wealthy populations), as well as the types of organizations (continuing concentration of ownership and control in large transnational corporations) (ICSWGSB 2011; ETC 2007; Redford *et al*. 2013). If patent "thickets" form in certain areas of synthetic biology applications, this could also restrict its accessibility by less wealthy countries (Redford *et al*. 2013). A strong concern of civil society groups is that strong IP regimes could also restrict access to information for carrying out independent, effective risk assessments (ICSWGSB 2011). Finally, it is possible that an additional challenge for conservation biologists and synthetic biologists to work together could be that the types of biological knowledge used by synthetic biologists are "much more restricted" (Redford *et al*. 2013).

Table 2. Examples of potential positive and negative impacts of synthetic biology with regard to social, economic and cultural considerations

Social, economic and cultural considerations	Possible positive and negative impacts of synthetic biology
Biosecurity	Synthetic biology techniques may provide tools for better detecting and identifying pathogenic agents, and responding to biosecurity threats, for example through accelerated vaccine production (Endy 2005; Mukunda et al. 2009; PCSBI 2010)
	Synthetic biology techniques may raise a "dual use" challenge, in that the substances used by research for positive ends may also be used for damaging results, such as creating destructive pathogens that target natural resources (Kaebnick 2009; Mukunda et al. 2009)
Economic	Synthetic biology is widely anticipated to play a significant role in the bioeconomy, which could benefit the economic growth (and human health and environment) of countries (EC 2012a; US White House 2012) Synthetic biology alternatives for natural products may lead to product displacement in developing countries, but potential harms may be addressed through product-specific arrangements and public engagement (Garfinkel & Friedman 2010; RAE 2009) or the natural version may still hold on to some share of the market, or the benefits of the synthetic biology versions may outweigh the losses (Wellhausen & Mukunda 2009) Products from synthetic biology, such as artemisinin, may improve the health of the people of developing countries and thus their economies (PCSBI 2010)
	Synthetic biology alternatives to natural products may lead to product displacement, harming the economies of developing countries and displacing the livelihoods of small-scale farmers and pickers (ETC 2013a; ICSWGSWB 2011) The necessary scale of extraction and use of biomass for a global economy may be ecologically unsustainable and rely on the same biomass resources as traditional economies (ETC 2011; Hall 2012; ICSWGSB 2011)
Health	Synthetic biology may: • help to study disease mechanisms (Lienert et al. 2014) • aid in diagnostics (PCSBI 2010) • aid in drug discovery through developing drug screening platforms (Pauwels et al. 2012) • help design organisms to produce drugs and vaccines (Dormitzer et al. 2013; Mueller et al. 2010; Ro et al. 2006) • help design therapeutic treatments (Khalil & Collins 2010; Wieland & Fussenegger 2012)

Source: Macroscopic Solutions, LLC

Source: Macroscopic Solutions, LLC

Table 2. continued	Examples of potential positive and negative impacts of synthetic biology with regard to social, economic and cultural considerations
Social, economic and cultural considerations	**Possible positive and negative impacts of synthetic biology**
Health	Synthetic biology applications may result in the possibility of direct harm to patients' health if engineered organisms / viruses trigger unanticipated adverse effects (König et al. 2013; PCSBI 2010) Synthetic biology may result in the possibility of direct harm for workers in synthetic biology laboratories (FOE et al. 2012; PCSBI 2010) Patent thickets and broad patents may restrict access to drugs and therapies (König et al. 2013)
Ethical	*Ethical discussions around synthetic biology are not structured around potential "positive" and "negative" impacts, but rather broad considerations*: Ethical analysis may help determine how to weigh and balance possible negative impacts of synthetic biology against possible positive impacts, as well as explore what equitable distribution of synthetic biology-related harms and benefits would look like and how to achieve this (Anderson *et al*. 2012; EGE 2009; Nuffield 2012; Parens *et al*. 2009) On the one hand, the ability to design significant portions of organisms may change humanity's approach to nature and lead humanity to overestimating our understanding of nature's processes (Boldt & Müller 2008); on the other hand, ethical discussions should not be based on assumptions that synthetic biology is able to do more than it can (Marris & Rose 2012) On the one hand, where synthetic biology research is based on a reductionist view of the world, it may undermine the special status of living things (Boldt & Müller 2008; Cho *et al*. 1999; ECNH 2010), on the other hand, "life" does not necessarily hold special status, and there is no evidence that synthetic biology science is leading to a "slippery slope" of devaluing some forms of life (ECNH 2010)
Intellectual property	A model of IP based on open-source software may lead to greater innovation, transparency, and openness (Calvert 2012) Using synthetic biology to design and synthesize DNA sequences may avoid ethical and legal challenges related to patenting natural DNA sequences (Torrance 2010)
	Synthetic biology may extend private ownership of genetic material, restricting access for public benefit (Redford *et al*. 2013; ECNH 2010; Schmidt *et al*. 2009) Strong IP regimes could restrict access to information for carrying out independent risk assessments (ICSWGSB 2011)

Source: Macroscopic Solutions, LLC

Source: PNNL

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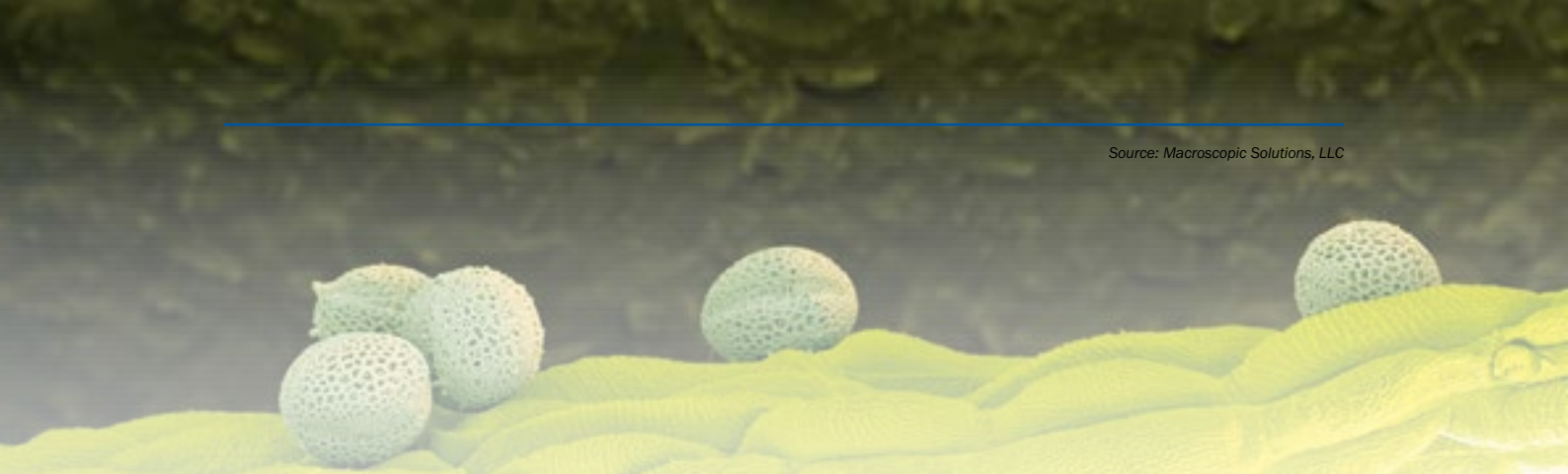

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PART II

POSSIBLE GAPS AND OVERLAPS WITH THE APPLICABLE PROVISIONS OF THE CONVENTION, ITS PROTOCOLS AND OTHER RELEVANT AGREEMENTS RELATED TO COMPONENTS, ORGANISMS AND PRODUCTS RESULTING FROM SYNTHETIC BIOLOGY TECHNIQUES

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A. EXECUTIVE SUMMARY

Overview

Synthetic biology as such has not been addressed in the text of multilateral treaties. However, a multitude of treaties, customary rules and general principles of law, as well as other regulatory instruments and mechanisms, could apply to all or some forms of what has been described as synthetic biology. Most of these treaties were developed before the term synthetic biology became widely used and, as such, only in a few cases contain explicit references to components, organisms and products resulting from synthetic biology techniques and their potential impacts. Depending on the circumstances, existing treaties may address: the transfer and handling of components, organisms and/or products resulting from synthetic biology techniques; the use of components, organisms and products resulting from synthetic biology techniques for a specific purpose, in particular for hostile purposes or in armed conflict; the rights associated with components, organisms and products resulting from synthetic biology techniques, e.g. patentability; and access to genetic resources used in synthetic biology techniques, and sharing of benefits arising from their utilization.

General rules of customary international law and treaties addressing the potential risks arising from the application of synthetic biology techniques

State responsibility describes the rules governing the general conditions under which a State is responsible for wrongful actions or omissions, and the resulting legal consequences. The rules on State responsibility require a breach of an obligation without defining these obligations. They provide only a general framework for addressing breaches of international law, including customary rules of international law and treaty obligations. The rules on State responsibility therefore do not address the conditions under which synthetic biology techniques would be permitted or prohibited. Under the rules on State responsibility, States are not as such responsible for acts for private actors unless one of the recognized relationships exists. However, a State might have to address the actions of private actors in order to fulfil its own obligation. A State could be in breach of an obligation if it fails to take necessary measures to prevent effects caused by private actors.

States are under a general obligation to ensure that activities within their jurisdiction or control respect the environment of other States or of areas beyond national jurisdiction or control. This duty to respect the environment does not mean, however, that *any* environmental harm, pollution, degradation or impact is generally prohibited. The duty prohibits a State from causing *significant transboundary* harm and obliges a State of origin to take adequate measures to control and regulate in advance sources of such potential harm. States have to exercise "due diligence" before carrying out potentially harmful activities. What constitutes "due diligence" would largely depend on the circumstances of each case. Establishing State responsibility for any harm from a synthetic biology technique would require that (i) the application of a synthetic biology technique can be attributed to a particular State and (ii) that it can be associated with a significant and particular harm to the environment of other States or of areas beyond national jurisdiction or control.

States have the duty to carry out an environmental impact assessment for activities that may have a significant adverse impact in a transboundary context, in particular, on a shared resource. An environmental impact assessment (EIA) is required in many domestic legal orders and the International Court of Justice has recently recognized that the accepted practice among States amounts to "a requirement under general international law". Thus, where there is a risk that a proposed industrial activity may have a significant adverse impact in a transboundary context, the requirement to carry out an environmental impact assessment applies even in the absence of a treaty obligation to this effect.

The precautionary principle or approach is relevant but its legal status and content in customary international law has not been clearly established, and the implications of its application to synthetic biology techniques are unclear. There is no uniform formulation or usage for the precautionary approach and its legal status in customary international law has not yet been clearly established, although it has been invoked several times by some States. The preamble of the Convention on Biological Diversity includes the following paragraph: "Noting also that where there is a threat of significant reduction or loss of biological diversity, lack of full scientific certainty should not be used as a reason for postponing measures to avoid or minimize such a threat". The Conference of the Parties, in decision XI/11, explicitly addressed the matter of synthetic biology and, recognizing the development of technologies associated with synthetic life, cells or genomes and the scientific uncertainties of their potential impact on the conservation and sustainable use of biological diversity, urged Parties and invited other Governments to take a precautionary approach, in accordance with the preamble of the Convention and with Article 14, when addressing threats of significant reduction or loss of biological diversity posed by organisms, components and products resulting from synthetic biology, in accordance with domestic legislation and other relevant international obligations. In its decisions addressing biofuels, the Conference of the Parties also urged Parties and other Governments to apply the precautionary approach to the introduction and use of living modified organisms for the production of biofuels as well as to the field release of synthetic life, cell, or genome into the environment, and to monitor technology associated with biofuels.

Living organisms resulting from current synthetic biology techniques are "living modified organisms resulting from biotechnololgy" as defined by the Convention on Biological Diversity and subject to its biosafety provisions (Articles 8(g) and 19). While its provisions on biosafety address potential negative impacts, the Convention also recognizes potential positive effects of biotechnology and provides for the access to and transfer of technologies, including biotechnology, that are relevant to the conservation and sustainable use of biological diversity. Where living modified organisms resulting from synthetic biology techniques are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health, Parties are required, as far as possible and as appropriate, to establish or maintain means to regulate, manage or control these risks at the national level. In addition, the Convention contains information sharing requirements for exporting countries.

Living organisms resulting from current synthetic biology techniques fall under the definition of "living modified organisms" under the Cartagena Protocol for Biosafety. Therefore, the requirements of the Cartagena Protocol pertaining to the transboundary movement, transit, handling and use of living modified organisms that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, also apply. Currently, living organisms resulting from synthetic biology techniques fulfil the criteria of (i) possessing a novel combination of genetic material, and (ii) resulting from the use of modern biotechnology and are, therefore, "living modified organisms" as defined in the Cartagena Protocol on Biosafety. The fulfillment of the above criteria may need to be reassessed if and when future technological advances of synthetic biology lead to the creation of living organisms possessing novel combinations of genetic material, which are heritable and do not result from the use of *in vitro* nucleic acid techniques or cell fusion. Some organisms resulting from synthetic biology techniques may fall under exemptions from the Advanced Informed Agreement provisions for living modified organisms, if they are in transit, intended for contained use or for direct use as food or feed, or for processing. The Cartagena Protocol will not apply to the transboundary movement of living organisms produced through synthetic biology that are pharmaceuticals for humans and addressed by other relevant international agreements or organizations. Although living organisms produced through synthetic biology may present characteristics that are not common to all living modified organisms, Annex III of the Protocol, including general principles, points to consider and methodology for risk assessment are still fully applicable to living organisms produced through synthetic biology and to products thereof, namely, "processed materials that are of living modified organism origin, containing detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology". To ensure the effective application of the provisions in Annex III, it may be necessary to identify elements of risk assessment methodologies that would be specific or particularly relevant to assessing the risks of living organisms developed through synthetic biology.

Once entered into force, the Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety will require Parties to provide at the national level for rules and procedures that

address damage from living modified organisms resulting from synthetic biology techniques, where such damage falls under the definition set out in Article 2 of the Supplementary Protocol.

The Biological Weapons Convention addresses, in part through legally-binding rights and obligations, microbial or other biological agents or toxins, including those which are components, organisms and products resulting from synthetic biology techniques, and provides a forum where further guidance for this aspect of synthetic biology could be developed. Parties to the Convention have confirmed that certain components, organisms and products resulting from synthetic biology techniques fall under the scope of "microbial or other biological agents, or toxins whatever their origin or method of production", which the Convention regulates. Where those agents or toxins are "of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes", the Convention, among others: (i) prohibits that its parties develop, produce, stockpile or otherwise acquire or retain them; (ii) requires its parties with those agents or toxins in their possession or under their jurisdiction or control, to destroy, or to divert them to peaceful purposes, (iii) prohibits their transfer; (iv) prohibits assisting, encouraging, or inducing any State, group of States or international organizations to manufacture or otherwise acquire them; and (v) requires its Parties to take necessary measures at the national level. In addition, the Convention contains the obligation to facilitate, and the right to participate in, the fullest possible exchange of equipment, materials and scientific and technological information, where they are used for peaceful purposes. Different meetings of the parties to the convention have acknowledged the potential positive and negative impacts from, among others, synthetic biology, and agreed on the value of promoting appropriate oversight measures to identify and manage risks, exploring approaches for developing guiding principles that could be tailored to national circumstances, sharing information about oversight frameworks, guiding principles, and practical experience, and the elaboration of models to inform risk assessment and oversight of scientific research activities that have significant dual-use potential, while promoting access to, and use of, the technologies they reviewed, including through the development of inexpensive and field-portable applications.

Some applications of synthetic biology could, depending on the specific case, be considered as causing risks to animal or plant life or health arising from the entry, establishment or spread of pests, diseases, disease-carrying organisms or disease-causing organisms; or as risks to human or animal life or health arising from additives, contaminants, toxins or disease-causing organisms in foods, beverages or feedstuffs. If this is the case, measures taken by WTO members to address these risks would count as sanitary and phytosanitary measures in the sense of the Agreement on the Application of Sanitary and Phytosanitary Measures of the World Trade Organization (SPS Agreement) and would have to comply with the requirements thereof. Measures that directly or indirectly affect international trade are allowed, as long as they are supported by a risk assessment or taken in accordance with international standards recognized under the SPS Agreement. The SPS Agreement explicitly recognizes the international standards, guidelines and recommendations developed by three organizations: For food safety the Codex Alimentarius Commission; for animal health and zoonoses the relevant international standards, guidelines and recommendations developed by the World Organisation for Animal Health (OIE); for plant health, those developed by the International Plant Protection Convention. In particular, components, organisms and products resulting from synthetic biology may be intentionally or unintentionally released to the environment, leading to biosafety concerns. Depending on the circumstances, they could be considered to pose risks to animal or plant life or health, through ecosystem-level impacts or the transfer of synthetic DNA. While guidance exists as to the application of standards to living modified organisms, it is not for all forms of synthetic biology techniques clear how these standards could be applied. The standard setting organizations Codex Alimentarius Commission, World Organisation for Animal Health or International Plant Protection Convention have not explicitly addressed synthetic biology.

Treaties addressing access to genetic resources, benefit-sharing from their utilization, and intellectual property rights that could be relevant to the application of synthetic biology techniques

In the cases where synthetic biology utilizes genetic resources and requires access to those resources, the access requirements of the Convention would, in general, apply and thus require prior informed consent (unless otherwise determined) and the negotiation of mutually agreed terms. Components used in synthetic biology include virtual/digital information on functional units of heredity. In this context, it is not clear whether the virtual/digital information about genes and other genetic elements can be considered "genetic resources" or "genetic material" in accordance with the definitions contained in Article 2 of the Convention. It is also unclear to what extent other components used in synthetic biology and the products thereof may be considered "genetic resources" as defined by the Convention.

Synthetic biology applications may be considered as a way of utilizing genetic resources as defined in the Nagoya Protocol. Synthetic biology also raises a number of questions in relation to the application of the Nagoya Protocol to derivatives. In this regard, it needs to be noted that there are different interpretations regarding how the Nagoya Protocol applies to derivatives. National implementation of the Nagoya Protocol can assist in further clarifying the definition of "utilization" as well as the scope of access and benefit-sharing requirements in relation to derivatives. The negotiation of mutually agreed terms can assist parties to an access and benefit-sharing agreement to clarify until which extent of the value chain the obligations to share benefits would continue to apply to components, organisms and products resulting from synthetic biology, including derivatives and their subsequent applications.

The International Treaty on Plant Genetic Resources for Food and Agriculture may be relevant to synthetic biology with regard to the access to genetic resources for use in synthetic biology processes and the sharing of the benefits arising from commercialization. Its Article 12 requires parties to provide facilitated access to plant genetic resources for food and agriculture to other parties, including to legal and natural persons under their jurisdiction. This access is to be granted pursuant to a standard material transfer agreement (MTA) through the Multilateral System under certain conditions. Synthetic biology research that does not include chemical, pharmaceutical and/or other non-food/feed industrial uses can access, in accordance with the relevant provisions of the ITPGRFA, the plant genetic resources for food and agriculture listed in Annex I to the treaty, a pool of 64 food and forage crops. These plant genetic resources cannot be protected through an intellectual property right in the form received from the Multilateral System. Under Article 13 of ITPGRFA Parties agreed that benefits arising from the use, including commercial, of plant genetic resources for food and agriculture under the Multilateral System shall be shared fairly and equitably through the exchange of information, access to and transfer of technology, capacity-building, and the sharing of the benefits arising from commercialization. The functioning and scope of the Multilateral System is currently under review by the Governing Body of the ITPGRFA.

It appears that, in accordance with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), patents should be available under national law of WTO members (other than LDCs) for innovative products and techniques in the field of synthetic biology, provided that they constitute inventions that comply with the general patentability standards. Select products of synthetic biology techniques may fall under the subject matter exclusions provided by Article 27, paragraphs 2 and 3 of the TRIPS Agreement and may therefore be excluded from patentability by some WTO members. The patentability of synthetic biology products and techniques may have both positive and negative implications, as it may encourage research and investments into and restrict access to and application of both technologies with potentially positive and potentially negative implications for biodiversity. The possibility to exclude certain synthetic biology products and techniques from patentability if prevention of their commercial exploitation is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, in accordance with Article 27, paragraphs 2 of the TRIPS Agreement may help to avoid some negative effects that may result from commercialisation of synthetic biology techniques.

The results of current synthetic biology research that is focused on modifying existing "natural" genomes could qualify for the "breeder's right" (a sui generis form of protection for intellectual property rights on plant varieties) under the UPOV Convention. As far as synthetic biology research may in the future result in the production of entirely novel genomes, it may be able to produce new plant varieties which could be protected by breeder's rights, including varieties that are deemed essentially derived from a protected variety.

Gaps in the current regulatory framework

Some general principles of international law such as the duty to avoid transboundary harm, and the need to conduct an environmental impact assessment (EIA), together with the rules of State responsibility may provide some guidance relevant to addressing potential negative impacts resulting from the application of synthetic biology techniques, but would still form an incomplete basis to address all potential negative impacts. Uncertainties exist with regard to their application in the absence of specific guidance. In addition, they may not be able to address the scope of the risks associated with some forms of synthetic biology techniques. Specific potential impacts of specific synthetic biology products might violate particular rules, but this cannot be determined unless there is greater confidence in estimates of such potential impacts.

Potential gaps may exist with regard to components and products resulting from synthetic biology techniques that are not living modified organisms. Such gaps could occur where components and products resulting from synthetic biology techniques do not fall within the scope of a treaty regime. For example, components and products resulting from synthetic biology techniques that are not living modified organisms will not be subject to the requirements pertaining to the transboundary movement, transit, handling

and use of all living modified organisms that may have adverse effects on the conservation and sustainable use of biological diversity contained in the Cartagena Protocol, nor the provisions on liability and redress contained in the Nagoya – Kuala Lumpur Supplementary Protocol.

A number of treaties exist which, in general, provide for mechanisms, procedures or institutions that can address potential negative effects associated with the application of synthetic biology techniques, but where no specific guidance exists for their application. Even though the requirements of the Cartagena Protocol pertaining to the transboundary movement, transit, handling and use of all living modified organisms that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, apply to most, if not all, organisms resulting from current synthetic biology techniques, it may be necessary, for example, to identify elements of risk assessment methodologies that would be specific for living organisms developed through synthetic biology in order to ensure the effective application of the provisions in Annex III to the Cartagena Protocol. As another example, States may be able to establish import restrictions on components, organisms and products resulting from synthetic biology techniques in accordance with the Agreement on the Application of Sanitary and Phytosanitary Measures of the World Trade Organization. However, while specific guidance has been developed for the application of standards to living modified organisms, for example under the International Plant Protection Convention, no such guidance exists for other components, organisms and products resulting from synthetic biology techniques.

In sum, the components, organisms and products resulting from synthetic biology would fall under the scope of a number of regulatory mechanisms. While some instruments are sufficiently broad to address some of the current issues related to synthetic biology, gaps still exist relating to the practical implementation of these instruments to ensure the conservation and sustainable use of biodiversity, and the fair and equitable sharing of the benefits arising from the utilization of genetic resources. Discussions in international fora may be needed with a view to addressing the gaps identified in this note in an appropriate, consistent, comprehensive and adaptive manner. This could include a need to consider how to address potential impacts of very low probability but very high magnitude. Further discussions may also be needed if and when the advances in synthetic biology lead to the emergence of new gaps.

Source: PNNL

Source: PNNL

B. SCOPE & METHODS

The Executive Secretary has been asked to consider possible gaps and overlaps with the applicable provisions of the Convention, its Protocols and other relevant agreements related to components, organisms and products resulting from synthetic biology techniques.

In response to this request, this document provides an overview of the provisions of the Convention, the Cartagena Protocol on Biosafety, the Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety and the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization, which may be particularly relevant for components, organisms and products resulting from synthetic biology techniques and their potential impacts on the conservation and sustainable use of biological diversity and associated social, economic and cultural considerations. Those impacts have been discussed in Part I of this document on potential positive and negative impacts of components, organisms and products resulting from synthetic biology techniques on the conservation and sustainable use of biodiversity.

In addition, the Executive Secretary was also required to consider "other agreements" which are part of the existing international regulatory framework that may be applicable to synthetic biology techniques. Apparently, synthetic biology as such has not been addressed in the text of multilateral treaties, while some treaty bodies have considered this issue. However, the international regulatory framework includes a multitude of treaties, actual and potential customary rules and general principles of law, as well as other regulatory instruments and mechanisms, that could apply to all or some forms of what has been described as synthetic biology. Therefore, this document discusses the following elements of the current international regulatory framework:

- International law and other principles that are generally applicable to States, and by virtue of their universal nature, are relevant to all synthetic biology techniques; and
- Provisions of the Convention, the Cartagena Protocol, the Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol and the Nagoya Protocol;
- Provisions of other treaties that may be applicable to synthetic biology techniques.

Most of these treaties were developed before the term synthetic biology became widely used and, as such, only in a few cases contain explicit references to components, organisms and products resulting from synthetic biology techniques and their potential impacts. For their respective Parties, they could apply, however, to:

- the transfer and handling of components, organisms and products resulting from synthetic biology techniques (Cartagena Protocol, Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol, Agreement on the Application of Sanitary and Phytosanitary Measures of the World Trade Organization, International Plant Protection Convention, standards of the World Organization for Animal Health, and the Codex Alimentarius);
- the use of components, organisms and products resulting from synthetic biology techniques for a specific purpose, in particular for hostile purposes or in armed conflict (Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction);
- rights associated with components, organisms and products resulting from synthetic biology techniques, e.g. patentability (Agreement on Trade Related Aspects of Intellectual Property Rights and International Convention for the Protection of New Varieties of Plants); and
- access to genetic resources used in synthetic biology techniques, and sharing of benefits arising from their utilization (Nagoya Protocol, International Treaty on Plant Genetic Resources for Food and Agriculture).

In order to assess gaps and overlaps in the existing international regulatory framework, this document examines the extent to which the Convention and its Protocols and other elements of the existing international legal framework explicitly or implicitly address components, organisms and products resulting from synthetic biology techniques and their potential impacts on the conservation and sustainable use of biological diversity and associated social, economic and cultural considerations as identified in Part I of this document on potential impacts. Acknowledging that *lex specialis* instruments are in many circumstances an appropriate mechanism for governing issues such as specific impacts on biodiversity from synthetic biology techniques, this document examines whether existing instruments, in *toto*, address all potential negative impacts resulting from the application of synthetic biology techniques.

As discussed in Part I of this document on potential impacts,[63] synthetic biology techniques may result in a wide variety of components, organisms and products and for a variety of uses. It is beyond the scope of the present document to discuss all international regulatory instruments that would apply to different products. This document only discusses the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction in the context of the use of products of synthetic biology techniques for a specific purpose, as synthetic biology has been discussed explicitly under this Convention.

Further, the scope of this document also excludes a discussion of national legal frameworks for synthetic biology. For example, extensive national regulations exist, which addresses pharmaceutical products and the exposure to hazardous chemicals. A number of reports are available where the legal frameworks of individual countries have been analyzed.[64]

This document draws as far as possible on published literature. Literature is available on the components, organisms and products resulting from synthetic biology and their potential impacts on the conservation and sustainable use of biological diversity and associated social, economic and cultural considerations (see Part I of this document on potential impacts) and also on the general scope and provisions of the elements of the existing regulatory framework discussed in this document (see list of references at the end of this document). Only a small number of publications, however, are available which apply the existing regulatory framework to synthetic biology.[65] The parts of this document that discuss the applicability of existing rules and treaty provisions to components, organisms and products resulting from synthetic biology therefore include partly an original analysis not part of peer-reviewed literature. It should be noted in this context that this document is made available for the information of Parties to the Convention and is not intended to affect the rights and obligations of Parties to the Convention or its Protocols.

Some aspects of the current international legal framework constitute binding rules within the meaning of Article 38 ICJ Statute. Binding rules include: treaties, customary law, and general principles of law. Other aspects are not legally binding but nonetheless provide guidance to States. Modern treaties often establish institutions and procedures in order to ensure implementation. This usually includes quasi-legislative bodies such as a Conference of the Parties to the treaty which has the mandate to decide on details not set out in the treaty and expert bodies which offer interpretations of treaty articles. Decisions taken by such quasi-legislative bodies are, as such, not binding unless the treaty so provides. However, decisions by meetings of the Conference of Parties may, as appropriate under the respective treaty, be referred to as an aid when interpreting the provisions of a treaty. Decisions of the meetings of the Conference of Parties decide on technical details that are unresolved by the treaty, and can specify how Parties are to implement and develop the regime.

Apart from existing rules and guidelines, it is important to keep in mind that many international regimes and institutions have a mandate that would allow them to address components, organisms and products resulting from synthetic biology, or some aspects of the topic in the future, even if they have not done so to date. In addition, there

63 *UNEP/CBD/COP/12/INF/11.*

64 *For example: C. Bailey, H. Metcalf, B. Crook and H. Hill. 2012. Synthetic Biology: A review of the technology, and current and future needs from the regulatory framework in Great Britain, Prepared by the Health and Safety Laboratory for the Health and Safety Executive. Accessible at http://www.hse.gov.uk/research/rrpdf/rr944.pdf; Presidential Commission for the Study of Bioethical Issues (PCSBI). 2010. New Directions: The Ethics of Synthetic Biology and Emerging Technologies. DC: PCSBI. Accessible at: www.bioethics.gov; S. Bar-Yam, J. Byers-Corbin, R. Casagrande, F. Eichler, A. Lin, M. Oesterreicher, P. Regardh, R.D. Turlington and K.A. Oye. 2012. The regulation of synthetic biology: A guide to United States and European Union regulations, rules and guidelines, SynBERC and iGEM Verion 9.1. Accessible at http://synberc.org/sites/default/files/Concise%20Guide%20to%20Synbio%20Regulation%20OYE%20Jan%202012_0.pdf; and S. R. Carter, M. Rodermeyer, M. S. Garfinkel, and R. M. Friedman. 2014. Synthetic Biology and the U.S. Biotechnology Regulatory System: Challenges and Options. J. Craig Venter Institute.*

65 *For example, OECD (2014), Emerging Policy Issues in Synthetic Biology, OECD Publishing. http://dx.doi.org/10.1787/9789264208421-en.*

Source: Macroscopic Solutions, LLC

are other instruments that could be of interest or relevance, regardless of their legal status. These include, for instance, self-organized standards by international organizations, the scientific community or recommendations by relevant civil society organisations. A number of international institutions have developed guidance around various aspects of biotechnology which may apply to synthetic biology research and applications, including:

- On biosafety: OECD 1986: Recombinant DNA Safety Considerations; OECD 1992: Safety Considerations for Biotechnology; FAO Voluntary Code of Conduct on Responsible Fisheries; UNIDO Voluntary Code of Conduct for the Release of Organisms into the Environment; UNEP International Technical Guidelines for Safety in Biotechnology; FAO 1996 - Code of Conduct for the Import and Release of Exotic Biological Control Agents;
- On access and benefit sharing: CGRFA - International Undertaking on Plant Genetic Resources; WHO 2011: Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits; FAO International Code of Conduct for Plant Germplasm Collecting and Transfer; and
- Codes of conduct for research: OECD 2007 Best Practices Guidelines for Biological Resource Centres; WHO 2012 Responsible life sciences research for global health security: A guidance document (biosafety and biosecurity); WHO Lab Biosafety Manual.

Source: Macroscopic Solutions, LLC

Source: IRRI

C. GENERAL RULES OF CUSTOMARY INTERNATIONAL LAW, TREATIES AND STANDARDS ADDRESSING THE POTENTIAL RISKS ARISING FROM THE APPLICATION OF SYNTHETIC BIOLOGY TECHNIQUES

Besides general rules of customary international law, the Convention, the Cartagena Protocol and its Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress, a number of other agreements and standards could be relevant to addressing the potential risks arising from the application of synthetic biology. They include the Biological Weapons Convention, the Agreement on the Application of Sanitary and Phytosanitary Measures of the World Trade Organisation, and the International Plant Protection Convention (IPPC).

1. INTERNATIONAL LAW AND PRINCIPLES APPLICABLE TO COMPONENTS, ORGANISMS AND PRODUCTS RESULTING FROM SYNTHETIC BIOLOGY[66]

International law includes a number of overarching rules and principles that are common legal ground and might apply to all activities related to components, organisms and products resulting from synthetic biology techniques. Treaties only apply to those States that are Party to them. In contrast, customary law applies to States regardless of whether they are a Party to, and bound by, a particular treaty.[67]

Some aspects of customary law, reviewed here, have a scope that may be relevant to components, organisms and products resulting from synthetic biology techniques. These rules and principles may, in particular, be discussed in the context of addressing potential negative effects from synthetic biology techniques. It will not be possible to draw specific conclusions on the extent to which these rules and principles will apply and have consequences for specific synthetic biology techniques, as this depends on the particularities of each specific case. A brief description of commonly discussed rules and principles that could apply to synthetic biology is nonetheless included in this document in order to illustrate their general limits.

It should be noted that the status of some concepts as legal principles or rules is disputed or their precise meaning is unclear.

66 *The descriptive parts of this chapter have been taken from the following study and have been adapted to the present document: Secretariat of the Convention on Biological Diversity (2012). Geoengineering in Relation to the Convention on Biological Diversity: Technical and Regulatory Matters, Montreal, Technical Series No. 66.*

67 *Except for so-called "persistent objectors".*

Source: PNNL

1.1. State responsibility and liability of private actors

State responsibility describes the rules governing the general conditions under which a State is responsible for wrongful actions or omissions, and the resulting legal consequences. The rules on State responsibility presuppose a breach of an international obligation by a State. However, the rules on State responsibility do not define the requirements of the obligation which is said to have been breached. Instead, they deal with the consequences of such breach.

The rules on State responsibility were codified and developed by the International Law Commission's Articles on Responsibility of States for Internationally Wrongful Acts, which for the most part reflect customary law (Annex to UNGA Res. A/RES/56/83 of 12.12.2001, "Articles on State Responsibility").[68]

The rules on State responsibility do not define obligations relating to synthetic biology in the sense that they determine which activities are permitted or prohibited. Instead, in the absence of specific rules, the rules on State responsibility provide a basic legal framework for activities related to synthetic biology in case they breach other existing international obligations.[69]

State responsibility does not as such require fault or negligence of the State. The conduct required or prohibited and the standards to be observed depend on the specific obligation in question. The consequences of State responsibility include legal obligations to cease the activity, to offer appropriate assurances and guarantees of non-repetition, if circumstances so require, and to make full reparation for the injury caused (Articles 30 and 31 of the Articles on State Responsibility).

The existence of "circumstances precluding wrongfulness", such as self-defence or force majeure (Chapter V of the Articles on State Responsibility), may preclude international responsibility notwithstanding a breach of an international obligation. One of these recognised circumstances is necessity. Article 25 reflects that "necessity may not be invoked by a State (…) unless the act is the only way for the State to safeguard an essential interest against a grave and imminent peril" and "does not seriously impair the essential interest of the State or States toward which the obligation exists, or to the international community as a whole." It further provides that "necessity may not be invoked by a State as a ground for precluding wrongfulness if (…) the State has contributed to the situation of necessity." (Article 25 of the Articles on State Responsibility). This may be relevant if synthetic biology techniques, as anticipated, are used to design and construct organisms with environmental functions such as bioremediation and pollution control (see section 5.2 of Part I of this document on potential impacts[70]). However, the fact-specific nature of circumstances precluding wrongfulness and their limitation to situations virtually beyond the control of a State limits their utility as an *ex ante* legal justification.

Synthetic biology techniques may be conducted by both State-governed and private entities. The customary international law of State responsibility, as reflected by the Articles on State Responsibility, addresses the circumstances under which the conduct of non-State actors may be attributable to a State. In general, the conduct of non-State actors is not attributable to a State unless one of the relationships outlined in the Draft Articles is present (e.g., a private actor exercising elements of governmental authority). Separately, a primary legal obligation (e.g., a treaty) may obligate a State to ensure the activities of its nationals conform to a certain standard, as in the example of Article 139 of the United Nations Convention on the Law of the Sea. A State could be in breach of an obligation

68 *The rules relevant to the present document are customary law, althoughsome other concepts in the Articles on State Responsibility may not be universally accepted. Previous drafts of the Articles on State Responsibility had introduced the concept of "international crimes", which included serious breaches of certain environmental obligations. However, that concept was subsequently dropped and does not appear in the final outcome of the ILC's work.*

69 *In addition, and as a result of a separate stream of work, the International Law Commission has also drafted a separate set of articles regarding harmful effects of "hazardous" acts, even where such acts are not in breach of an international obligation, although such principles only refer to the allocation of loss, see for instance the work of the ILC on Draft Articles on Prevention of Transboundary Harm from Hazardous Activities, UN Doc A/56/10. This could include making private actors liable under domestic law, cf. ILC, Draft principles on the allocation of loss in the case of transboundary harm arising out of hazardous activities, UN Doc. A/66/10, paragraph 66, in particular principle 4.2. In contrast to many of the Articles on State Responsibility, these draft articles do not reflect customary law.*

70 *UNEP/CBD/COP/12/INF/11.*

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if it fails to take necessary measures to prevent effects caused by private actors. It depends on the obligation in question to what extent a State has to address private actors in order to fulfil its own obligation.

In addition, a State can be under an explicit and specific obligation to address private actors. Specifically, international law can impose a duty on States to provide in their internal law that non state actors are liable for certain acts. For instance, the 2010 Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety requires States to address private actors through domestic rules on liability. However, there is no general obligation on States to do this.

1.2. Prevention of transboundary harm to the environment

The International Court of Justice, in the *Gabcikovo-Nagymaros* case, and in its advisory opinion on the *Legality of the Threat or Use of Nuclear Weapons*, confirmed the "existence of the general obligation of States to ensure that activities within their jurisdiction and control respect the environment of other States or of areas beyond national control is now part of the corpus of international law relating to the environment."[71] In the *Pulp Mills* case, the Court used a slightly different wording:[72] "It is 'every State's obligation not to allow knowingly its territory to be used for acts contrary to the rights of other States' (Corfu Channel (United Kingdom v. Albania), Merits, Judgment, I.C.J. Reports 1949, p. 22). A State is thus obliged to use all the means at its disposal in order to avoid activities which take place in its territory, or in any area under its jurisdiction, causing significant damage to the environment of another State." The Court further clarified that "the principle of prevention, as a customary rule, has its origins in the due diligence that is required of a State in its territory."[73]

Article 3 of the Convention, entitled "Principle", states that "States have in accordance with the Charter of the United Nations and the principles of international law the sovereign right to exploit their own resources pursuant to their own environmental policies, and the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction". Principle 2 of the Rio Declaration contains similar language.[74]

The duty not to cause transboundary harm does not mean that any environmental harm, pollution, degradation or impact is for that reason generally prohibited (Birnie *et al*. 2009). Considering the differences in wording used when referring to the duty not to cause transboundary harm, the precise content of this duty has not been defined. From the wording used by the ICJ in the *Pulp Mills* case, it appears that an alleged breach of the duty to not harm the environment, establishing responsibility of a State for an activity related to synthetic biology would require the following elements:

- Significant damage to the environment of another State;
- Activity caused by the State in question / lack of due diligence;
- No circumstances precluding wrongfulness (see section 1.1 above).

Many synthetic biology research and commercial applications have the potential for transboundary impacts through economic, social, and cultural impacts. Direct impacts on the transboundary environment, however, would depend on the specific application of synthetic biology. Currently, intentional environmental release of organisms resulting from synthetic biology techniques seem to be limited to a few instances such as the Glowing Plant, which will be distributed within the United States (see section 4.2.5 of Part I of this document on potential impacts[75]). Anticipated applications of synthetic biology include the production of micro-organisms

71 *ICJ, Case concerning the Gabcikovo-Nagymaros Project (Hungary v. Slovakia), ICJ Reports 1997, 7, paragraph 53; and Legality of the Threat or Use of Nuclear Weapons (Advisory Opinion - General Assembly), ICJ Reports 1996, 22, paragraph 29.*

72 *The earliest version of this concept can be found in the Trail Smelter Arbitration, where the arbitral tribunal stated that "under principles of international law (...) no State has the right to use or permit of its territory in such a manner as to cause injury by fumes on or in the territory of another or the properties therein, if the case is of serious consequence and the injury is established by clear and convincing evidence", see Trail Smelter Arbitration (United States v. Canada, Reports of International Arbitral Awards, vol.3, 1938 (1941), p. 1965).*

73 *ICJ, Case concerning Pulp Mills on the River Uruguay (Argentia v. Uruguay), ICJ Reports 2010, 14, paragraph 101.*

74 *31 ILM 876 (1992); cf. principle 21 of the preceding 1972 Declaration of the UN Conference on the Human Environment (Stockholm Declaration), 11 ILM 1416 (1972).*

75 *UNEP/CBD/COP/12/INF/11.*

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specifically designed for environmental release, such as for bioremediation of ocean oil spills (see section 5.2 of Part I of this document on potential impacts). Alleged environmental harm could, for example, also include that organisms resulting from synthetic biology techniques displace existing species because of engineered fitness advantages and become invasive (Redford *et al*. 2013; Snow and Smith 2012; Wright *et al*. 2013).

While the wording of Article 3 of the Convention requires "damage", the wording of the ICJ in the *Pulp Mills* case requires "significant damage". For both cases it is not clear what degree of environmental harm would constitute such damage. "Significant" could be understood to establish a *de minimis* threshold and to require a certain intensity of damage, which appears to be more than just any damage. Whether damage caused by synthetic biology techniques is "significant" will have to be established for the particular case in question.[76]

While the ICJ did not elaborate on the specific requirements for causality, a potential claimant State may have to establish a causal link between the particular synthetic biology activity and, for example, the displacement of a certain species.

In the *Pulp Mills* case, the ICJ also appears to require an element of due diligence, providing for a prohibitive function of the duty not to cause transboundary harm.[77] According to this view, the concept obliges every State of origin to take adequate measures to control and regulate in advance sources of potential significant transboundary harm." (Beyerlin and Marauhn 2011). It is, however, not clear which measures States are required to take in order to prevent such harm. Generally, a State will not be in breach of the obligation relevant here unless it fails to apply due diligence.[78] What diligence is "due", however, depends on the circumstances of the particular case related to components, organisms and products resulting from synthetic biology techniques.

In sum, the obligation to prevent transboundary harm depends on the particularities of the specific case and is mainly retrospective. International law provides only very limited means to obtain advance provisional measures in order to stop activities that could be in breach of international obligations.[79] Therefore, the duty not to cause transboundary harm may not be a sufficient instrument to address potential negative impacts from synthetic biology techniques, in particular potential impacts of very low probability but very high magnitude.

1.3. Duty to undertake an environmental impact assessment

A further general rule which may be considered to address potential negative impacts resulting from synthetic biology techniques is the duty to carry out an environmental impact assessment.

While Article 14 of the Convention also addresses environmental impact assessment, the requirement to carry out an environmental impact assessment for industrial activities that may have a significant adverse impact *in a transboundary context* has even become customary international law and applies to States in the absence of treaty obligations. The ICJ has recently recognized that the accepted practice amongst States amounted to "a requirement under general international law to undertake an environmental impact assessment where there is

76 *The Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety provides, in its Article 4, a list of factors as basis for determining whether a particular damage is "significant", see section 2.3.4 below.*

77 *Note that the exact relationship between the two dimensions of the no harm concept is still subject to a significant degree of unclarity. All sources seem to agree though that the obligation to prevent represents an essential aspect of the obligation not to cause significant harm. (Handl 2007).*

78 *Cf. ILC, Articles on State Responsibility, UN Doc. A/56/10, para 77, Chapter III para 2; ILC, Draft articles on prevention of transboundary harm from hazardous activities, UN Doc. A/56/10, paragraph 98, Article 3 paragraph 8.*

79 *In recent years the ICJ has only granted two applications for provisional measures, in cases involving the imminent execution of prisoners, LaGrand Case (Germany v. United States of America), Provisional Measures, order of 03.03.1999; Avena and Other Mexican Nationals (Mexico v. United States of America), order of 05.02.2003. All other applications were rejected, see Armed Activities on the Territory of the Congo (New Application: 2002) (Democratic Republic of the Congo v. Rwanda), order of 10.07.2002; Certain Criminal Proceedings in France (Republic of the Congo v. France), order of 17.06.2003; Pulp Mills on the River Uruguay (Argentina v. Uruguay), orders of 13.07.2006 and 23.01.2007; Questions relating to the Obligation to Prosecute or Extradite (Belgium v. Senegal), order of 28.05.2009; Proceedings instituted by the Republic of Costa Rica against the Republic of Nicaragua, press release of 19.11.2010; all available at http://www.icj-cij.org.*

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a risk that the proposed industrial activity may have a significant adverse impact in a transboundary context, in particular, on a shared resource".[80]

As discussed in the previous section, some of the potential applications of synthetic biology could result in transboundary impacts and could in certain cases have the potential to cause significant adverse impacts.[81] The ICJ referred to activities that "may" have a significant adverse impact. However, it does not establish a threshold of probability for "may."

Independently of the required threshold, it is a matter of disagreement among synthetic biologists, ecologists, industry and civil society, how well the potential dangers related to synthetic biology are known and can be assessed. Some synthetic biologists and the Biotechnology Industry Organization have argued that the vast majority of synthetic biology research does not present novel risks and that sufficient knowledge is available to characterize associated risks (de Lorenzo 2010; Erickson *et al*. 2011). Others, however, are much more cautious about the potential unanticipated risks of synthetic biology (Dana *et al*. 2012; FOE *et al*. 2012; ICSWGSB 2011; Snow and Smith 2012; Tucker and Zilinskas 2006). In their comment in *Nature*, Dana *et al*. (2012) call for a minimal investment of 20-30 million USD in synthetic biology risk research over the next 10 years. They state: "No one yet understands the risks that synthetic organisms pose to the environment, what kinds of information are needed to support rigorous assessments, or who should collect such data" (Dana *et al*. 2012). One of the four identified areas of necessary risk research is how microbes could alter habitats, food webs, and biodiversity (Dana *et al*. 2012).

Significant adverse impacts that may occur include low-probability and high-consequence. In a March 2013 *Science* editorial, Martin Rees, former president of the UK Royal Society, identified synthetic biology as a potential existential threat, albeit in a "sci-fi scenario (Rees 2013).[82]

The ICJ left it to the States to determine the specific content of the impact assessment required. It specified the following details:

- The duty to carry out an environmental impact assessment for industrial activities that may have a significant adverse impact in a transboundary context involves "having regard to the nature and magnitude of the proposed development and its likely adverse impact on the environment as well as to the need to exercise due diligence in conducting such an assessment."
- The impact assessment has to be carried out prior to the implementation of the activity.
- Continuous monitoring of the activity's effect on the environment is required.

As a legal rule in customary international law, the duty to carry out an environmental impact assessment for industrial activities that may have a significant adverse impact in a transboundary context is an important development that might require clarification as to its precise implications.

1.4. Precautionary approach

The Conference of the Parties to the Convention, in paragraph 4 of decision XI/11, urged Parties and invited other Governments to take a precautionary approach, in accordance with the preamble and with Article 14 of the Convention, when addressing threats of significant reduction or loss of biological diversity posed by organisms, components and products resulting from synthetic biology, in accordance with domestic legislation and other relevant international obligations.

Several multilateral environmental treaties and other instruments include precaution under various labels, such as "precautionary principle", "a precautionary approach", "the precautionary approach" or "precautionary measures". Some States refer to

80 *ICJ, Case concerning Pulp Mills on the River Uruguay (Argentia v. Uruguay), ICJ Reports 2010, paragraphs 204 -206.*

81 *In a comment to an earlier draft of this document, a Party noted its opinion that, while applications of synthetic biology (or other biotechnology) involving micro-organisms for intentional release "add a layer of complexity to the risk assessment", "addressing potential challenges in environmental risk assessment is premature since environmental applications of synthetic biology are not expected to materialize before several years." Another reviewer noted, however, that the fact that we do not yet know enough (or have the right monitoring infrastructure) to carry out good environmental impact assessments of many synthetic biology applications calls for the development of the knowledge and techniques to carry out such assessments.*

82 *Rees writes: "Synthetic biology likewise offers huge potential for medicine and agriculture, but in the sci-fi scenario where new organisms can be routinely created, the ecology (and even our species) might not long survive unscathed....Some would dismiss such concerns as an exaggerated jeremiad: After all, societies have survived for millennia, despite storms, earthquakes, and pestilence. But these human-induced threats are different—they are newly emergent, so we have a limited time base for exposure to them and can't be so sanguine that we would survive them for long, or that governments could cope if disaster strikes. That is why a group of natural and social scientists in Cambridge, UK, plans to inaugurate a research program to identify the most genuine of these emergent risks and assess how to enhance resilience against them" (Rees 2013).*

Source: Macroscopic Solutions, LLC

a "precautionary principle", while others consider that formulations of precaution are too varied to be referred to as a "principle". Under the Convention, a precautionary approach has been introduced in the preamble recognizing that "where there is a threat of significant reduction or loss of biological diversity, lack of full scientific certainty should not be used as a reason for postponing measures to avoid or minimize such a threat". The decisions of the Conference of the Parties have frequently been based on and stressed the importance of the precautionary approach (see for example decisions II/10, V/8 and IX/20).

There is no uniform formulation or usage for the precautionary approach and its legal status in customary international law has not been clearly established, although it has been invoked several times (Beyerlin and Marauhn 2011).

2. CONVENTION ON BIOLOGICAL DIVERSITY

The objectives of the Convention on Biological Diversity are: the conservation of biological diversity, the sustainable use of its components, and access to genetic resources and the fair and equitable sharing of the benefits arising out of their utilization (Article 1). The Convention text does not specifically refer to synthetic biology. Depending on the scope of synthetic biology's definition, the following Convention provisions could be relevant[83]:

2.1. Principle of the Convention (Article 3)

Article 3 of the Convention provides that "States have in accordance with the Charter of the United Nations and the principles of international law the sovereign right to exploit their own resources pursuant to their own environmental policies, and the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction". For a discussion of this principle in the context of synthetic biology techniques see section 1.2 above.

2.2. Impact assessment and minimizing adverse impacts (Article 14(a) and (b))

Article 14(a) of the Convention commits each Party to, as far as possible and as appropriate, "introduce appropriate procedures requiring environmental impact assessment of its proposed projects that are likely to have significant adverse effects on biological diversity (…)." Article 14(b) requires each Party, as far as possible and as appropriate, to "introduce appropriate arrangements to ensure that the environmental consequences of its programmes and policies that are likely to have significant adverse impacts on biological diversity are duly taken into account".

This provision requires Parties that do not have procedures for environmental impact assessments for their proposed projects, which are likely to cause significant adverse effects on biological diversity, to introduce such procedures (Glowka *et al*. 1994).

Where synthetic biology projects are projects of a Party and are likely to have significant adverse effects on biological diversity, they should be covered by the environmental impact assessment procedures required by Article 14(a).

The Convention does not define further what is understood by "likely" and "significant". As noted in section 1.2 above, "significant" could be understood to establish a *de minimis* threshold and to require a certain intensity of impact. As has been discussed above, the probability of potential negative impacts of synthetic biology techniques is for many applications not clear. In addition, the interpretation of "likely" and "significant" may also have to take into account the case of low-probability, high-impact scenarios which some synthetic biology applications may pose.

2.3. Biosafety provisions associated with LMOs (Article 8(g) and 19(4))

The majority of the Convention's work on biosafety has focused on the negotiation, in response to Article 19, paragraph 3 of the Convention, and subsequent on-going implementation of the Cartagena Protocol on Biosafety (SCBD 2005). The Convention itself addresses biosafety through Articles 8(g) and 19, paragraph 4.

Article 8(g) requires Parties, as far as possible and as appropriate, to "establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect

83 *Articles 15 and 16-19 are discussed in section 3.1 below.*

the conservation and sustainable use of biological diversity, taking also into account the risks to human health." Article 19, paragraph 4 states that Parties shall provide any available information about their use and safety regulations in handling any living modified organism resulting from biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity, as well as any available information on the potential adverse impact of the specific organisms concerned to a Party into which those organisms are to be introduced.

"Biotechnology" is defined in Article 2 of the Convention as any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use (Article 2). According to the IUCN *Guide to the Convention on Biological Diversity*, this definition was "designed to include both present and future technologies and processes" (Glowka *et al*. 1994). The Convention does not define "biological systems," "living organisms," or "derivatives thereof" (see Article 2). According to Cartagena Protocol (Article 3(i)), "modern biotechnology" is defined as the application of: (a) in vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or (b) fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.

Synthetic biology is widely referred to as a type of "biotechnology" (Nuffield 2012; Garfinkel *et al*. 2007; Heinemann and Panke 2006). Much of the synthetic biology research and most of its commercialized products involve the use of living organisms, and thus it would be classified as biotechnology as defined by the Convention.

The extent to which biosafety provisions of the Convention apply to synthetic biology depends on the interpretation of "living modified organisms resulting from biotechnology"; "likely to have adverse environmental impacts" and "potential adverse impacts", and "use and release", which are discussed in the following sections.

2.3.1. "Living modified organisms"

The text of the Convention does not define "living modified organisms." According to the IUCN *Guide to the Convention*, negotiators replaced the term "genetically modified organisms" with "living modified organisms" in order to broaden the scope of obligations under the relevant articles (Glowka *et al*. 1994). Unlike the Cartagena Protocol's definition of living modified organisms (see section 2.3), which applies to organisms obtained through the use of *modern* biotechnology, the Convention's use of the term is meant to include organisms whose genetic material is modified through traditional techniques, such as selective breeding and artificial insemination, as well as "organisms whose genetic material is more directly modified through, for example, recombinant DNA technology" (Glowka *et al*. 1994).

The Convention does not define "living organisms" either; the Cartagena Protocol defines "living organism" as "any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids" (Article 3(h) Cartagena Protocol). Whether an organism resulting from synthetic biology techniques would be considered a living modified organism in the context of the Convention might depend on which products of synthetic biology are considered as "living":[84] The areas of research that are considered "synthetic biology" include DNA-based circuits, synthetic metabolic pathway engineering, synthetic genomics, protocell construction, and xenobiology:

- **DNA-based circuits** involve the rational design of sequences of DNA to create biological circuits with predictable, discrete functions, which can then be combined in modular fashion in various cell hosts. Genetic circuits are seen to function in a manner analogous to electronic logic components, like switches and oscillators;
- **Synthetic metabolic pathway engineering** aims to redesign or rebuild metabolic pathways, to synthesize a specific molecule from the "cell factory." A synthetic pathway (typically based on naturally occurring DNA sequences that are computer 'optimized') is added to the cell, and then classic genetic engineering tools may be used to increase the desired output;
- **Synthetic genomics** focuses on the genome as the "causal engine" of the cell. Top-down synthetic genomics starts with a whole genome, from which researchers gradually remove "non-essential" genes to pare down to the smallest possible genome size at which the cell can function as desired. The primary goal is to craft a simplified "chassis" to which modular DNA "parts" can be added. Bottom-up synthetic genomics aims to build functional genomes from pieces of synthesized DNA. At this point, natural genomes are needed as models because of the many DNA sequences that are necessary but have unknown functions;

84 *As noted in tPart I of this document on potential impacts, some areas of synthetic biology are still at the basic research stage, notably protocell construction and xenobiology.*

Source: Macroscopic Solutions, LLC

- **Protocell construction** aims to create the simplest possible components to sustain reproduction, self-maintenance, metabolism and evolution. Thus this research seeks to design for less complexity at the cellular level (rather than at the genome level as in the case of genome-level engineering);
- **Xenobiology** (also known as chemical synthetic biology) is the study and development of life forms based on biochemistry not found in nature. Xenobiology aims to alter DNA and RNA to produce XNA (xeno-nucleic acids) and novel proteins. Xenobiology is often cited as a potential "built-in" biocontainment mechanism to prevent gene transfer to wild organisms.

2.3.2. "Are likely to have adverse environmental impacts" / "potential adverse impacts"

Both Articles 8(g) and 19, paragraph 4 use probability-based language - "are likely to have adverse environmental impacts" and "potential adverse impacts". An initial matter of interpretation is establishing the thresholds of probability for "likely" and "may." The IUCN *Guide to the Convention* suggests that assessing the likelihood of risk could be guided by three primary criteria: (i) familiarity with the organism and its characteristics; (ii) the organism's contemplated application; and (iii) the environment into which the organism will or could be released (Glowka *et al*. 1994).

The Cartagena Protocol on Biosafety may also be relevant in this regard. According to its Article 15 and Annex III on risk assessment, the purpose of conducting a risk assessment under the Protocol is to identify and evaluate the "potential adverse effects" of LMOs on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also into account risks to human health. Paragraph 8 of Annex III outlines a number of steps to meet this objective, providing that a risk assessment is entailed, as appropriate:

- An identification of any novel genotypic and phenotypic characteristics associated with the living modified organism that may have adverse effects on biological diversity in the likely potential receiving environment, taking also into account risks to human health;
- An evaluation of the likelihood of these adverse effects being realized, taking into account the level and kind of exposure of the likely potential receiving environment to the living modified organism;
- An evaluation of the consequences should these adverse effects be realized;
- An estimation of the overall risk posed by the living modified organism based on the evaluation of the likelihood and consequences of the identified adverse effects being realized;
- A recommendation as to whether or not the risks are acceptable or manageable, including, where necessary, identification of strategies to manage these risks; and
- Where there is uncertainty regarding the level of risk, it may be addressed by requesting further information on the specific issues of concern or by implementing appropriate risk management strategies and/or monitoring the living modified organism in the receiving environment.

As discussed in section 1.3 above, it is a matter of disagreement among synthetic biologists, ecologists, industry, and civil society, on how well the potential dangers related to synthetic biology are known and can be assessed.

2.3.3. "Use and release of living modified organisms

Article 8(g) addresses "risks associated with the use and release" of living modified organisms. One possible interpretation of this text is that *two* categories of risks are included – risks associated with the use of living modified organisms and risks associated with the release of living modified organisms. The text could also be interpreted to consider only those risks associated with both the use *and* release of living modified organisms.

Some anticipated future uses of synthetic biology may require environmental release, and would thus seem to fall within this aspect of Article 8(g). Current commercial and industrial uses of synthetic biology are primarily organisms resulting from synthetic metabolic engineering that perform specific industrial processes (such as enzymes to degrade biomass) or produce specific compounds (such as yeast producing artemisinic acid). With some notable exceptions, the organisms resulting from synthetic biology techniques themselves are not currently on the market or meant for environmental release (see sections 3 and 5 of Part I of this document on potential impacts on near term and existing products).[85] There are, however, wide variations in the kinds of and degree of containment, for example, synthetically-modified algae that may be grown in

85 *The International Civil Society Working Group on Synthetic Biology (ICSWGSB) recommends that the Conference of the Parties urge Parties to "ensure that synthetic genetic parts and living modified organisms produced by synthetic biology are not released into the environment or approved for commercial use until there is an adequate scientific basis on which to justify such activities and due consideration is given to the associated risks for biological diversity, also including socio-economic risks and risks to the environment, human health, livelihoods, culture and traditional knowledge, practices and innovations" (ICSWGSB 2011). In comments to an earlier draft of this document, an organization noted that the terms "adequate scientific basis" and "due consideration" are subjective and need to be further defined.*

Source: Macroscopic Solutions, LLC

open ponds to micro-organisms used in decentralized bioreactors that may be prone to leakage (Marris and Jefferson 2013).

In sum, many of the examples of organisms developed through synthetic biology can be considered as "living modified organisms resulting from biotechnology" as defined by the Convention on Biological Diversity and, as such, would be subject to its biosafety provisions as per Articles 8(g) and 19.

2.3.4 Decisions of the Conference of the Parties referring to synthetic biology

Two decisions of the Conference of the Parties refer directly to synthetic biology. The relevant paragraphs are as follows:

- Decision X/37 "Biofuels and biodiversity", paragraph 16: "The COP urges Parties and other Governments to apply the precautionary approach in accordance with the Preamble to the Convention, and the Cartagena Protocol, to the introduction and use of living modified organisms for the production of biofuels as well as to the field release of synthetic life, cell, or genome into the environment, acknowledging the entitlement of Parties, in accordance with domestic legislation, to suspend the release of synthetic life, cell, or genome into the environment."
- Decision XI/11 "New and emerging issues relating to the conservation and sustainable use of biodiversity", paragraph 4: "The COP, *recognizing* the development of technologies associated with synthetic life, cells or genomes, and the scientific uncertainties of their potential impact on the conservation and sustainable use of biological diversity, urges Parties and invites other Governments to take a precautionary approach, in accordance with the preamble of the Convention and with Article 14, when addressing threats of significant reduction or loss of biological diversity posed by organisms, components and products resulting from synthetic biology, in accordance with domestic legislation and other relevant international obligations."

A further decision that may be interpreted as referring to synthetic biology:

- Decision XI/27 "Biofuels and biodiversity", paragraph 6: "The COP, *recognizing also* the rapidly developing technology associated with biofuels, urges Parties and other Governments to monitor these developments, and recalls decision IX/2, paragraph 3(c)(i), which urged Parties and invited other Governments, inter alia, to apply the precautionary approach in accordance with the preamble of the Convention on Biological Diversity."

3. CARTAGENA PROTOCOL ON BIOSAFETY

The Cartagena Protocol on Biosafety (Cartagena Protocol) applies to the transboundary movement, transit, handling and use of all living modified organisms (LMOs) that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health (Article 4 Cartagena Protocol). Article 1 of the Cartagena Protocol explicitly refers to the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development. The Cartagena Protocol has 167 Parties and entered into force in 2003.

In 2012, the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management of the Cartagena Protocol identified the risk assessment of LMOs produced through synthetic biology among a set of topics for the development of further guidance (CPB AHTEG 2012, Annex IV). This was "noted" by the sixth meeting of the Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety (COP-MOP 6), which also established a new AHTEG on Risk Assessment and Risk Management to "Consider the development of guidance on new topics of risk assessment and risk management, selected on the basis of the Parties' needs and their experiences and knowledge concerning risk assessment" (BS-VI/12 Annex 1(c)). In 2014, the AHTEG on Risk Assessment and Risk Management once again identified the risk assessment of LMOs produced through synthetic biology as a possible topic for the development of further guidance.[86]

This section first examines which organisms and products of synthetic biology might be considered as LMOs in the context of the Cartagena Protocol. The applicability of exemptions to certain Cartagena Protocol provisions are considered for LMOs produced through synthetic biology, as based on current and near-term research and commercialization of synthetic biology. Risk assessments undertaken pursuant to the Cartagena Protocol must be carried out in accordance with Annex III (Article 15 Cartagena Protocol); the general principles, methodology, and points to consider of Annex III are examined for application to synthetic biology.

86 Document UNEP/CBD/BS/AHTEG-RA&RM/5/6, paragraph 38(h).

3.1. LMOs and components, organisms and products of synthetic biology

The Cartagena Protocol defines LMOs as "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology" (Article 3(g) Cartagena Protocol). To be considered LMOs, the applications of synthetic biology would thus have to: i) be a living organism, ii) possess a novel combination of genetic material, and iii) result from the use of modern biotechnology. It should be stressed that these terms are intrinsically interlinked, such that a novel combination of genetic material that did not result from the use of modern biotechnology would not be considered an LMO in the context of the Cartagena Protocol.

3.1.1. Living organisms

The Cartagena Protocol defines a "living organism" as "any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids" (Article 3(h) Cartagena Protocol). "Genetic material" is not defined in the Cartagena Protocol; in the Convention it is defined as any material "containing functional units of heredity" (Article 2). Given this definition, many areas of research in synthetic biology would be considered as producing living organisms, including microbes produced by genome-level engineering and cells altered by synthetic metabolic engineering (see section 2.3.1 above).

Two outstanding questions regarding the scope of "living organisms" in the relation to current uses of synthetic biology are: i) products of organisms resulting from synthetic biology techniques; and ii) naked DNA and constituent parts.

3.1.1.1 Products of organisms resulting from synthetic biology techniques

According to the IUCN *Explanatory Guide* to the Cartagena Protocol on Biosafety, the products of LMOs (referred to as "products thereof") were extensively discussed during the negotiations of the Cartagena Protocol (Mackenzie *et al*. 2003). "Products thereof" in the context of the Cartagena Protocol seem to primarily refer to LMOs that have been processed. They are included in notifications under Annex I and risk assessments under Annex III if they contain "detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology" (Article 20, paragraph 3(c); Annex I, paragraph (i); and Annex III, paragraph 5 Cartagena Protocol).

Organisms resulting from synthetic biology techniques that are currently used for commercial purposes are largely micro-organisms that have been altered to produce specific compounds, such as specialized chemicals, fuels, flavors, and pharmaceuticals (Wellhausen and Mukunda 2009). The compounds are not simply processed LMOs; they are the by-products of microbes or microbial fermentation of biomass. They may fall within the Protocol's definition of "products thereof" if they contain nucleic acids containing a novel combination of genetic material. However, products that are in commercial use, such as vanillin and artemisinic acid, are generally highly refined and would not be expected to contain nucleic acids.

3.1.1.2 DNA and constituent parts

The situation is less clear with regard to DNA and constituent parts. According to the IUCN *Explanatory Guide to the Carta gena Protocol on Biosafety*, the consensus decision was to not directly include plasmids or DNA in the Article 3(h) definition of living organisms (Mackenzie *et al*. 2003). DNA and parts produced for synthetic biology have been transported through postal mail for decades. For example, New England BioLabs Inc. offers the BioBrick Assembly Kit for sale over the internet. Components of the kit include destination plasmids and the upstream and downstream parts as purified DNA.[87] Purified DNA is also mailed from commercial DNA synthesis firms, often in a lyophilized (freeze-dried) form. Furthermore, because long stretches of DNA can be fragile, commercial DNA synthesis firms sometimes incorporate gene- and genome-length pieces of DNA into more stable DNA molecules (e.g. artificial chromosones) and living cells for shipment (Garfinkel *et al*. 2007). If novel DNA is inserted into living cells for shipment, those cells seem to clearly qualify as "living organisms" as per the Cartagena Protocol. Otherwise, "naked" DNA and parts may not qualify as "living organisms" under the Cartagena Protocol.

The Cartagena Protocol provisions on risk assessment and the minimum required information to be included in notifications under some of the Protocol's procedures may apply to naked DNA and its constituent parts resulting from synthetic biology techniques if they contain "detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology" (Annex I(i); and Annex III, paragraph 5 Cartagena Protocol).

87 *Ginkgo BioWorks and New England BioLabs Inc. Undated. BioBricktm Assembly Manual: Version 1.0. Available at http://ginkgobioworks.com/support/BioBrick_Assembly_Manual.pdf, accessed 6 March 2013.*

88 *Changes can be deliberate, as in "watermark" sequences of DNA or "codon optimized" sections, or accidental (see: Gibson et al. 2010).*

In practice, however, many countries do not apply the Cartagena Protocol's provisions on risk assessment and the minimum required information to naked DNA and its constituent parts because they are considered to be components rather than products of LMOs.

3.1.2. Novel combination

A "novel combination of genetic material" can result from a novel *form* or a novel *arrangement* of the functional units of heredity, regardless of whether or not this leads to a phenotypic change (Mackenzie *et al*. 2003). Most applications of synthetic biology are focused on producing novel genetic materials. Organisms resulting from synthetic biology techniques modeled after natural organisms (such as the Spanish influenza virus and the JCVI bacterial genome) are not exact copies of the originals, and thus would qualify as novel.[88] The use of directed evolution techniques that do not incorporate new genetic material, such as "gene shuffling," would likely still be considered to result in 'novel combinations' because they rearrange existing genetic material (Mackenzie *et al*. 2003).

3.1.3. Modern biotechnology

As stated in section 2.3 above, "modern biotechnology" is defined in the Cartagena Protocol as:

> "the application of:
>
> a. *In vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or
>
> b. Fusion of cells beyond the taxonomic family,
>
> that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection" (Article 3(i) Cartagena Protocol).

The negotiators of the Cartagena Protocol recognized that new techniques for modifying genetic information would continue to be developed (Mackenzie *et al*. 2003). According to the IUCN explanatory guide, although the definition gives two specific examples of *in vitro* nucleic acid techniques, other techniques cannot be excluded from the definition so long as they overcome natural physiological reproductive or recombination barriers and are not techniques used in traditional breeding and selection. The techniques and tools of synthetic biology represent an expanding frontier of biotechnology, but current applications can be considered to remain within the Cartagena Protocol's definition of modern biotechnology.

3.2. Possible exemptions to certain provisions of the Cartagena Protocol

The Cartagena Protocol applies to the transboundary movement, transit, handling and use of all LMOs that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health (Article 4 Cartagena Protocol). The text provides limited exemptions of some LMOs to some provisions, as outlined in the following subsections.

3.2.1 Exclusion from provisions of the Cartagena Protocol: pharmaceuticals for humans that are addressed by other relevant international agreements or organizations (Article 5)

The Cartagena Protocol does "not apply to the transboundary movement of living modified organisms which are pharmaceuticals for humans that are addressed by other relevant international agreements or organizations" (Article 5 Cartagena Protocol). According to the Biotechnology Industry Organization (BIO), synthetic biology is already being used to produce pharmaceuticals for humans. Synthetic biology and directed evolution technology were used by Codexis to discover and develop a transaminase to enable a biocatalytic route for the production of Sitagliptin, a treatment for type II diabetes marketed as Januvia by Merck (BIO 2013). The pharmaceutical company, DSM has also used synthetic biology to improve the process of the commercial production of the antibiotic, Cephalexin, by introducing and optimizing genes in a penicillin-producing microbial strain (*Ibid*). Furthermore Sanofi intends to produce 35 tons of "semi-synthetic"[89] artemisinin for malaria treatment in 2013 (Sanofi and PATH 2013). In 2013, researchers at Novartis and Synthetic Genomics published an approach to rapidly generate influenza vaccine viruses, using an enzymatic, cell-free gene assembly technique, producing an accurate vaccine more quickly than previously possible (Dormitzer *et al*. 2013). Another approach referred to as "SAVE" (synthetic attenuated virus engineering) (Coleman *et al*. 2008) was used to rationally redesign the genome of an influenza virus, resulting in an attenuated virus with hundreds of nucleotide changes (Mueller *et al*. 2010). Still at the research stage are synthetic biology devices that would provide therapeutic treatment, for example

89 *The term "semi-synthetic" is used because Sanofi has developed a proprietary photochemical method to convert artemisinic acid into artemisinin (Sanders 2013).*

through reprogramming mammalian cells to tackle diseases through prosthetic gene networks (see Wieland & Fussenegger 2012), controlling the timed delivery of drugs, and more controlled approaches to gene therapy (see Khalil & Collins 2010). Synthetic biology techniques are anticipated to play a major role in future pharmaceutical development and production (RAE 2009).

Where synthetic biology organisms are being used as "biofactories" to produce pharmaceuticals such as in the case of artemisinin; the organisms themselves are not pharmaceuticals. These organisms therefore are not eligible for exemption under Article 5 (see Mackenzie *et al*. 2003). Vaccines produced using synthetic biology techniques, however, would likely be considered pharmaceuticals under Article 5 of the Cartagena Protocol.[90] Future advances in synthetic biology, such as gene therapy through artificial chromosomes and modifying bacteria and viruses to identify malignant cells and deliver therapeutic agents may be considered pharmaceuticals.

LMOs that are pharmaceuticals for humans must also be addressed by other relevant international agreements or organizations to be exempted from the Cartagena Protocol. It is unclear to what extent LMOs that are pharmaceuticals for humans would need to be "addressed" by other international agreement or organization to qualify for the Article 5 exemption. In particular, it is an open question whether the agreement or organization must address the biodiversity impacts of the LMO (Mackenzie *et al*. 2003).

Currently, none of the organisms produced through synthetic biology that are intended to be used as pharmaceuticals for humans are directly addressed by other relevant international agreements or organizations. For example, a commonly invoked promise of synthetic biology is the rapid development of vaccines using viruses (RAE 2009; PCSBI 2010). Therefore, such living organisms would fall under the Cartagena Protocol's scope.

3.2.2. Exemptions from the Advanced Informed Agreement provisions

There are limited exemptions to the requirements of the Advance Informed Agreement procedure (Article 7 Cartagena Protocol).

3.2.2.1 "Contained use" (Article 6)

Under the Cartagena Protocol, provisions for Advanced Informed Agreement (AIA) do not apply to the transboundary movement of LMOs "destined for contained use undertaken in accordance with the standards of the Party of import" (Article 6, paragraph 2 Cartagena Protocol).[91] Contained use is defined as an operation, "undertaken within a facility, installation or other physical structure," in which the LMOs' contact with and impact on the external environment is "effectively limit(ed)" by "specific measures" (Article 3(b) Cartagena Protocol). Negotiations on this topic concentrated on whether chemical or biological barriers could be considered as sufficient containment, or whether physical containment was necessary (van der Meer 2002; Mackenzie *et al*. 2003). Ultimately, the text focuses on the *effectiveness* of containment measures, rather than the type of measure. The question of degree and quality of effectiveness is also left up to the Party to determine (Mackenzie *et al*. 2003).

At least three issues have been raised by some civil society groups in relation to synthetic biology and the "contained use" AIA exemption. First, the ICSWGSB (2011) argues that containment facilities that Parties consider to effectively contain LMOs may be unsuitable to contain organisms resulting from synthetic biology techniques.[92] Importing countries may need advance information in order to "judge the effectiveness of available containment" (*Ibid*). The ICSWSB calls on the Convention of the Parties serving as the meeting of the Parties to the Protocol (COP-MOP) to exclude synthetic genetic parts and LMOs produced by synthetic biology from the "contained use" exemption under the AIA provisions "at least until effective containment methods can be demonstrated" (*Ibid*). Some comments received on an earlier draft to this document strongly question the claim that containment strategies for organisms resulting from synthetic biology techniques would need to be different from those for other LMOs.

A second issue is whether specific members of the synthetic biology community should be considered able to provide for "contained use." EcoNexus, a European civil society group, has raised doubts as to whether DIYbio (do-it-yourself biology) individuals and collectives can ever be considered a "contained use" operation (EcoNexus 2011). EcoNexus does

90 *The IUCN Guide to the Cartagena Protocol reports that living modified organisms that are pharmaceuticals for humans are "principally genetically engineered vaccines" (Mackenzie et al. 2003). In comments to an earlier version of this document, one organization noted that "continued research and development of vaccines, whether for humans or animals, may be discouraged if synthetic biology is further included within the Cartagena Protocol."*

91 *The Cartagena Protocol does not require that Parties regulate such LMOs according to the AIA provisions, but Parties are still free to use national legislation to require AIA and risk assessment (Mackenzie et al. 2003).*

92 *This concern is premised on the ICSWGSB's view that organisms resulting from synthetic biology techniques, such as de novo organisms designed and constructed in the lab, may be significantly different from other organisms, including conventionally genetically-modified organisms, in that they lack analogs in the natural world (ICSWGSB 2011).*

not consider "garage biotech facilities" as contained use, and is concerned that AIA "might become close to impossible" in such instances (EcoNexus 2011). The recent WWICS report on DIYbio found that 92% of DIYers work in group spaces (not alone), that few DIYers are using "sophisticated" synthetic biology, and most work in labs that are rated as Biological Safety Level 1 (Grushkin *et al*. 2013). Considering the current status of the synthetic biology practiced by DIYers, the WWICS report finds that DIYers present a low risk to the environment. It does, however, note that future boundaries between home and group labs may be porous, leading to experiments being carried in transit and possibly spilling, and issues around the disposal of lab waste (Grushkin *et al*. 2013). These are issues around contained use, although again, Grushkin *et al*. (2013) do not see these as current problems, but possible future concerns depending on the development of synthetic biology and the DIYbio communities.

A third and more general issue, which is not limited to LMOs produced by synthetic biology, is that Parties could be faced with "regulatory arbitrage" if a laboratory imports a synthetic biology LMO for contained use and then makes a domestic application to release the synthetic biology LMO from containment (ICSWGSB 2011). Domestic standards for risk assessment may be lower than the minimums provided in the Cartagena Protocol's Annex III. The ICSWGSB recommends that the Cartagena Protocol be revised such that "any agent receiving an LMO into containment without obtaining prior informed consent may only release that LMO after it has been approved under a risk assessment process at least as strong as that specified in Annex III" (ICSWGSB 2011).

3.2.2.2 LMOs "intended for direct use as food or feed, or for processing" (Article 11)

The AIA procedure does not apply to the transboundary movement of LMOs intended for direct use as food or feed, or for processing (LMO-FFPs), although developing country Parties or Parties with an economy in transition may, in the absence of a domestic regulatory framework, declare through the Biosafety Clearing-House that their decision prior to the first import of an LMO-FFP will be taken according to a risk assessment and a decision made within a predictable timeframe (Article 7, paragraph 2 and Article 11, paragraph 6 Cartagena Protocol). Furthermore, a Party that makes a final decision regarding domestic use of an LMO that may be subject to transboundary movement for direct use as food or feed, or for processing is to inform Parties through the Biosafety Clearing-House and this information is to include a risk assessment report consistent with Annex III of the Protocol (Article 11, paragraph 1 and Annex II (j) Cartagena Protocol). LMO-FFPs must be accompanied by documentation that "clearly identifies that they "may contain" living modified organisms and are not intended for intentional introduction into the environment" (Article 18, paragraph 2(a) Cartagena Protocol). Different procedures apply, therefore, as documentation requirements vary according to the nature of the LMO concerned and its intended use in the Party of import (Mackenzie *et al*. 2003).

3.2.3. LMOs that may be identified by the COP-MOP as "not likely to have adverse effects" (Article 7(4))

The Cartagena Protocol provides opportunities for Parties to cooperate to identify LMOs that are "not likely to have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health" (Article 7, paragraph 4 Cartagena Protocol). Parties must formally identify an LMO that is "not likely to have adverse effects" through a COP-MOP decision. Such LMOs would then be exempted from the AIA procedure (Article 7, paragraph 4 Cartagena Protocol). To date, the COP-MOP has not identified any LMO that is "not likely to have adverse effects." In 2012, Parties to the Cartagena Protocol were invited to provide the Executive Secretary with "scientific information that may assist in the identification of living modified organisms or specific traits that may have or that are not likely to have adverse effects" (BS-VI/12, paragraph 11).[93] The Executive Secretary was requested to create sections in the Biosafety Clearing-House where the information could be submitted and easily retrieved (BS-VI/12, paragraph 12).

3.3. Application of Annex III Risk Assessment to synthetic biology

Under Article 15, paragraph 2, a risk assessment must be carried out for a Party of import to make a decision as per Article 10 for an intentional transboundary movement to proceed (Article 10 and Article 15, paragraph 2, Cartagena Protocol). Risk assessments must be "carried out in a scientifically sound manner, in accordance with Annex III and taking into account recognized risk assessment techniques" (Article 15, paragraph 1 Cartagena Protocol). A risk assessment as per Annex III is

93 *When considering risk management Parties shall also cooperate to identify LMOs or specific traits of LMOs that "may have adverse effects," and "take appropriate measures" regarding their treatment (Article 16, paragraph 5 Cartagena Protocol). This provision also asks Parties to make an assessment of the likelihood of impacts. As with Article 7, paragraph 4, Parties have not yet identified any LMOs or traits that fall under this category.*

Source: Macroscopic Solutions, LLC

also required if a developing country Party or a Party with an economy in transition that does not have a domestic regulatory framework decides to import an LMO-FFP and has indicated that its decision prior to import will be taken on this basis (Article 11, paragraph 6(a) Cartagena Protocol).

Annex III of the Cartagena Protocol provides general principles, methodology, and points to consider in a risk assessment. The methodology of a risk assessment as per Annex III requires: hazard identification; evaluation of likelihood of effects; evaluation of consequences of those effects if they occur; and characterization of risks based on the likelihood and consequences of effects (Annex III, paragraph 8, Cartagena Protocol). The risk assessment may take into account the characteristics of the recipient organisms, donor organisms, receiving environment, the introduced modification, and the identity of the LMO (Annex III, paragraph 9, Cartagena Protocol). The Parties have also developed further guidance on risk assessment of living modified organisms including a roadmap for risk assessment of LMOs that supplements Annex III of the Protocol as well as guidance on the risk assessment of specific types of LMOs and traits as well as the monitoring of LMOs released into the environment.[94]

Although LMOs produced through synthetic biology may present characteristics that are not common to all LMOs, Annex III of the Protocol, including its general principles, points to consider and methodology are still fully applicable to living organisms produced through synthetic biology and may also apply to "products thereof" that contain "detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology" (Article 20, paragraph 3(c), Annex I(i); and Annex III, paragraph 5 Cartagena Protocol).

In addition, it could be discussed whether the risk assessment process of Annex III, which is based on the characteristics of the recipient and donor organisms and the added traits, might be adequate for synthetic biology organisms that have been developed to include genetic material from several donor organisms that may have also been optimised. In these cases, there might not be an appropriate comparator. One author considers that in this context that the risk assessment process outlined in Annex III of the Cartagena Protocol "cannot deal with such biocircuit systems" (Schmidt 2009). Unlike conventional genetic engineering techniques, synthetic biology may make the transfer of "whole systems," rather than single traits, possible. The reliance on the consideration of individual traits may be insufficient, because it is the interactions among the parts that has "no comparable counterpart in nature, making it more difficult to predict the cell's full behavioral range with a high degree of certainty" (Ibid.). Schmidt asks whether the characteristics of such a network can be predicted to a degree of certainty that would allow a "reasonable estimation" of risk (Ibid.). He identifies a number of challenges to standard risk assessment, including what will happen when one or several parts evolve to change their functions, and how to measure robustness and reliability in the case of biological circuits. Schmidt's response is not to suggest adaptations in risk assessment methods, but rather to suggest potential biosafety engineering options in designing biocircuits, such as Event Tree Analysis and Fault Tree Analysis. The ICSWGSB's analysis of the Cartagena Protocol finds that Annex III's risk assessment procedures are inadequate – particularly in cases where biological parts and devices do not have an analog in the natural world (ICSWGSB 2011).

3.4. Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety

The objective of the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol (Supplementary Protocol) is to contribute to the conservation and sustainable use of biological diversity, taking also into account risks to human health, by providing international rules and procedures in the field of liability and redress relating to living modified organisms.

The issue of liability and redress for damage resulting from the transboundary movements of LMOs was one of the themes on the agenda during the negotiation of the Biosafety Protocol. The negotiators were, however, unable to reach any consensus regarding the details of a liability regime under the Protocol. In 2010, the Conference of the Parties serving as the meeting to the Parties to the Cartagena Protocol adopted the Supplementary Protocol. It has not yet entered into force.

This Supplementary Protocol applies to damage resulting from living modified organisms which find their origin in a transboundary movement and are (i) intended for direct use as food, feed, or for processing; (ii) destined for contained use; or (iii) intended for intentional introduction into the

94 The "Guidance on Risk Assessment of Living Modified Organisms" is available via http://bch.cbd.int/onlineconferences/guidance_ra.shtml.

Source: Macroscopic Solutions, LLC

environment (Article 3 Supplementary Protocol). It applies to damage resulting from any authorized use of the living modified organisms, damage resulting from unintentional transboundary movements as referred to in Article 17 of the Cartagena Protocol, as well as damage resulting from illegal transboundary movements as referred to in Article 25 of the Cartagena Protocol.

The Supplementary Protocol provides in Article 12 that Parties shall provide, in their domestic law, for rules and procedures that address damage. "Damage" is defined by the Supplementary Protocol (Article 2) as an adverse effect on the conservation and sustainable use of biological diversity, taking also into account risks to human health, that is measurable or otherwise observable taking into account, wherever available, scientifically-established baselines recognized by a competent authority that takes into account any other human induced variation and natural variation. Whether an adverse effect is "significant" is to be determined on the basis of factors, such as (i) the long-term or permanent change, to be understood as change that will not be redressed through natural recovery within a reasonable period of time; (ii) the extent of the qualitative or quantitative changes that adversely affect the components of biological diversity; (iii) the reduction of the ability of components of biological diversity to provide goods and services; and (iv) the extent of any adverse effects on human health in the context of the Protocol. A causal link needs to be established between the damage and the living modified organism in question in accordance with domestic law (Article 4 Supplementary Protocol).

As discussed in section 3.1 above, organisms resulting from synthetic biology techniques may fall under the definition of a "living modified organism" under the Cartagena Protocol. Further, as described in 5 of Part I of this document, it is possible that living modified organisms resulting from synthetic biology techniques could cause adverse effects on the conservation and sustainable use of biological diversity. For example, unintentionally released organisms may transfer the inserted genetic material and thus change biodiversity at a genetic level, intentionally released organisms may become invasive due to engineered fitness advantages. As has been discussed, there appears to be significant controversy as to the scope and therefore "significance" of the potential damages. The applicability of the provisions of the Supplementary Protocol would have to be assessed for particular cases.

Once entered into force, the Supplementary Protocol will require Parties to provide, in their domestic law, for rules and procedures that address damage from organisms resulting from synthetic biology techniques, where such damage falls under the definition set out in Article 2 of the Supplementary Protocol.

4. CONVENTION ON THE PROHIBITION OF THE DEVELOPMENT, PRODUCTION AND STOCKPILING OF BACTERIOLOGICAL (BIOLOGICAL) AND TOXIN WEAPONS AND ON THEIR DESTRUCTION

The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (Biological Weapons Convention – BWC) entered into force in 1975 and currently has 168 Parties. This agreement may apply to the use of components, organisms and products resulting from synthetic biology techniques for hostile purposes or in armed conflict.[95]

4.1. Overview of main provisions

The core provision of the Biological Weapons Convention is its Article 1 in which each Party to this Convention undertakes never in any circumstance to develop, produce, stockpile or otherwise acquire or retain: (i) microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; or (ii) weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.

Further, where such agents, toxins, weapons, equipment and means of delivery are in the possession or under the jurisdiction and control of a Party, the Party is obliged to destroy or divert them

95 *Relevant in this context is also the Australia Group, an informal forum of countries which, through the harmonisation of export controls, seeks to ensure that exports do not contribute to the development of chemical or biological weapons. The 41 states participating in the Australia Group are parties to the Chemical Weapons Convention and the Biological Weapons Convention. Coordination of national export control measures assists Australia Group participants to fulfil their obligations under those conventions. The Australia Group meets annually to discuss ways of increasing the effectiveness of participating countries' national export licensing measures to prevent potential proliferators from obtaining materials for chemical or biological weapons programs. Since 2007, meetings of the Australia Group have discussed synthetic biology, see www.australiagroup.net.*

Source: Macroscopic Solutions, LLC

to peaceful purposes not later than nine months after the entry into force of the Convention (Article II BWC). Article III prohibits the transfer of agents, toxins, weapons, equipment and means of delivery to any recipient, and Article IV requires each Party to take any necessary measures at the national level to prohibit and prevent the development, production, stockpiling, acquisition or retention of the agents, toxins, weapons, equipment and means of delivery. Other provisions address consultation among Parties (Article V BWC), establish a complaint system (Article VI BWC) and assistance in the case of a violation of obligations under the Convention (Article VII BWC).

Article X of the Biological Weapons Convention requires its Parties to facilitate, and have the right to participate in, the fullest possible exchange of equipment, materials and scientific and technological information for the use of bacteriological (biological) agents and toxins for peaceful purposes. It also states that the Biological Weapons Convention has to be implemented in a manner designed to avoid hampering the economic or technological development of its Parties or international cooperation in the field of peaceful bacteriological (biological) activities, including the international exchange of bacteriological (biological) agents and toxins and equipment for the processing, use or production of bacteriological (biological) agents and toxins for peaceful purposes in accordance with the provisions of the Convention.

4.2. Microbial or other biological agents, or toxins

The described obligations can apply to components, organisms and products resulting from synthetic biology techniques as far as they are microbial or other biological agents, or toxins. This matter has been addressed by a number of Review Conferences under the Biological Weapons Convention.[96]

The Second Review Conference reiterated that "the Convention unequivocally applies to all natural or artificially created microbial or other biological agents or toxins whatever their origin or method of production. Consequently, toxins (both proteinaceous and non-proteinaceous) of a microbial, animal or vegetable nature and their synthetically produced analogues are covered" (BWC 1986).

The Sixth Review Conference in 2006 adopted a final declaration covering the full scope of the Convention which stated "that the Convention is comprehensive in its scope and that all naturally or artificially created or altered microbial and other biological agents and toxins, as well as their components, regardless of their origin and method of production and whether they affect humans, animals or plants, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes, are unequivocally covered by Article I"; and further that "Article I applies to all scientific and technological developments in the life sciences and in other fields of science relevant to the Convention" (BWC 2006). Thus, any of the areas of synthetic biology research and techniques of synthetic biology would be covered if used to produce such agents or toxins.

The Seventh Review Conference in 2012 reaffirmed this scope and included in the 2012-2015 intersessional programme of the Convention a standing agenda item on review of developments in the field of science and technology related to the Convention.[97]

4.3. Prophylactic, protective or other peaceful purposes

The prohibition in Article I of the Biological Weapons Convention to develop, produce, stockpile or otherwise acquire or retain biological agents and toxins is not absolute. It applies only to types and to quantities that have no justification for prophylactic, protective or other peaceful purposes. During the negotiations of the Convention, it was clarified that the term "prophylactic" encompasses medical activities, such as diagnosis, therapy and immunization, whereas the term "protective" covers the development of protective masks and clothing, air and water filtration systems, detection and warning devices, and decontamination equipment, and must not be interpreted as permitting possession of biological agents and toxins for defence, retaliation or deterrence. The term "other peaceful purposes" was not defined during the negotiations, but may be understood to include scientific experimentation (Goldblat 1997). For the use of bacteriological (biological) agents and toxins for the described peaceful purposes, Article X of the Biological Weapons Convention applies – the obligation to facilitate, and the right to participate in, the fullest possible exchange of equipment, materials and scientific and technological information.

96 A Review Conference is a conference of State Parties, which, in accordance with Article XII of the Convention reviews the operation of the Convention and also considers, among others, new scientific and technological developments relevant to the Convention.

97 For references to working documents under the Biological Weapons Convention that address synthetic biology, see UNICRI 2011.

Source: Macroscopic Solutions, LLC

4.4. Relevant conclusions by intersessional meetings of State Parties

The meeting of the States Parties to the Biological Weapons Convention in 2012 reviewed various enabling technologies, including: bioinformatics; computational biology; DNA microarrays; gene synthesis technology; high-throughput mass spectrometry; high-throughput sequencing; nanotechnology; synthetic biology; systems biology; and whole-genome directed evolution. Parties agreed that these developments could provide for faster, cheaper, and easier application of biological science and technology (BWC 2012, paragraph 28).

Parties identified opportunities for maximising benefits from these enabling technologies while minimizing risks of their application for prohibited purposes, including, for example, supporting (BWC 2012, paragraph 31):

- Efforts to ensure the fullest possible exchange of equipment, materials and scientific and technological information and in full conformity with the provisions of the Convention;
- Enhanced national oversight of dual use research of concern without hampering the fullest possible exchange of knowledge and technology for peaceful purposes;
- Continued discussion under the Convention on oversight of dual use research of concern;
- Improved use by relevant national agencies of available sequence and function data;
- Enhanced reference databases to support identification of agents by relevant national agencies; and
- Promotion of the beneficial applications of gene synthesis technologies while ensuring their use is fully consistent with the peaceful object and purpose of the Convention.

Parties recognized that the Convention is relevant to an increasing convergence of scientific disciplines, in particular biology and chemistry. They also noted the value of using codes of conduct on a voluntary basis and of various national measures (BWC 2012, paragraph 33), such as:

- Promoting interaction between relevant national agencies and the scientific community;
- Strengthening linkages between biosafety and biosecurity training and broader issues of responsible conduct;
- Encouraging the addition of relevant elements to existing codes, where they exist, as an alternative to developing new codes;
- Supporting the inclusion of relevant material in professional training courses;
- Encouraging the development of practical tools for use by individuals and organizations to familiarize them with the provisions of the Convention; as well as
- Enabling specific outreach for those working outside of institutional research and commercial environments.

At their meeting in 2013, Parties identified certain developments in science and technology that have potential benefits for the Convention and agreed on the need to share information on these developments, including (BWC 2013, paragraph 29):

- Improving identification of biological agents and toxins for both health and security purposes, resulting from advances in life science research, including metagenomics, immunological methods, molecular probes, amplification of nucleic acids, and in microbial forensics;
- Advances in comparative genomics, which would increase the capacity to investigate alleged use of biological weapons;
- Improved, more efficient and economical vaccine and diagnostic technologies, resulting from advances in:
    - Identifying new targets and reducing the timescale for the development of vaccines, drugs and diagnostics;
    - Production of vaccines including through developments in single-use or disposable bioreactor systems, which can increase yield, cost-effectiveness, portability and safety, and novel vaccine production methods, including cell cultures and cell suspension bioreactors, recombinant DNA, metabolic engineering and synthetic biology, chemical peptide synthesis; and transgenic animals and plants;
    - Vaccine distribution and delivery, such as encapsulation in silk matrices, nano-vesicles, and nanotechnology-based patches;
    - Point-of-care diagnostic systems suitable for use in low resource settings resulting from advances in microfluidics, nanotechnology, lateral flow immunoassays and new techniques emerging from multidisciplinary collaborations that combine different approaches into simple devices;
- Enhanced epidemiological capacity including for identifying unknown pathogens, outbreak sources and animal reservoirs, resulting from advances in faster and less expensive high-throughput DNA sequencing, along with parallel advances in computational biology.

At the same meeting, Parties also noted the value of a number of activities in order to further seize opportunities for maximizing benefits from advances in science and technology while minimizing the risk of their application for prohibited purposes, including (BWC 2013, paragraph 31):

- Promoting access to, and use of, the technologies they reviewed, including through the development of inexpensive and field-portable applications;
- Promoting appropriate oversight measures to identify and manage such risks, ensuring that they are proportional to the assessed risk, take into account both risks and benefits, and avoid hampering legitimate peaceful activities;
- Recognizing that a one-size-fits-all approach is unsuitable, exploring approaches for developing guiding principles that could be tailored to national circumstances;
- Undertaking efforts to engage the scientific community, research funding organizations and, when appropriate, industry in dialogue about how best to identify and manage these risks;
- Sharing information about oversight frameworks, guiding principles, and practical experience with other States Parties;
- Continuing discussion under the Convention on dual use research, bringing in a wide range of national and international stakeholders and focusing on specific instances in order to better understand options for mitigating risks; and
- The elaboration of models to inform risk assessment and oversight of scientific research activities that have significant dual-use potential, which should be carried out during all phases of the research cycle.

However, no concrete steps towards the development of an oversight framework, guiding principles, or models to inform risk assessment and oversight of scientific research have been undertaken to date.

5. THE AGREEMENT ON THE APPLICATION OF SANITARY AND PHYTOSANITARY MEASURES (THE "SPS AGREEMENT")

The Agreement on the Application of Sanitary and Phytosanitary Measures of the World Trade Organization (SPS Agreement) is part of the system of multilateral trade rules of the World Trade Organization (WTO). The SPS Agreement attempts to strike a balance between, on one hand, reaffirming the rights of WTO members to adopt and enforce measures that are necessary to protect human, animal or plant life or health, and, on the other hand, making sure that these measures are not excessively trade restrictive. The SPS Agreement applies to all sanitary and phytosanitary measures that directly or indirectly affect international trade (Article 1 SPS Agreement).

5.1. Sanitary or phytosanitary measures

Sanitary or phytosanitary measures can take many forms, including laws, decrees, regulations, requirements; testing, inspection, certification and approval procedures; quarantine treatments; requirements associated with the transport of animals or plants; sampling procedures; and methods of risk assessment. The SPS Agreement defines sanitary and phytosanitary measures as any measure applied with one of the following objectives (Article 1, paragraph 2 in conjunction with Annex A, paragraph 1 SPS Agreement):

- to protect animal or plant life or health within the territory of the Member from risks arising from the entry, establishment or spread of pests, diseases, disease-carrying organisms or disease-causing organisms;
- to protect human or animal life or health within the territory of the Member from risks arising from additives, contaminants, toxins or disease-causing organisms in foods, beverages or feedstuffs;
- to protect human life or health within the territory of the Member from risks arising from diseases carried by animals, plants or products thereof, or from the entry, establishment or spread of pests; or
- to prevent or limit other damage within the territory of the Member from the entry, establishment or spread of pests.

WTO members have the right to take sanitary and phytosanitary measures that are necessary for the protection of human, animal or plant life or health, even if these measures result in trade restrictions. However, these measures have to be consistent with the provisions of the SPS Agreement (Article 2, paragraph 1 SPS Agreement). Requirements include, for example, that the measures must be based on scientific principles, must not unjustifiably discriminate in their effect on other WTO members' exports, and must not be more trade-restrictive than is necessary to achieve the appropriate level of

sanitary or phytosanitary protection (Articles 2, 3 and 5 SPS Agreement).

The SPS Agreement encourages WTO members to harmonize their sanitary and phytosanitary measures on the basis of international standards, guidelines and recommendations, since harmonization reduces costs for producers and traders and generally facilitates trade. Sanitary and phytosanitary measures that conform to international standards, guidelines or recommendations are deemed to be necessary to protect health, and are presumed to be consistent with the SPS Agreement. For such measures that conform to international standards, WTO members thus e.g. do not have to provide a scientific justification.

The SPS Agreement explicitly recognizes the international standards, guidelines and recommendations developed by three organizations: for food safety, the Codex Alimentarius Commission; for animal health and zoonoses, the relevant international standards, guidelines and recommendations developed by the World Organisation for Animal Health (OIE); for plant health, those developed by the International Plant Protection Convention (IPPC). For matters not covered by these three organizations, there is a possibility that the Committee on Sanitary and Phytosanitary Measures under the SPS Agreement could identify standards developed by other relevant international organizations, but so far there has never been a proposal to recognize another standard-setting body.

If no relevant international standard exists, or when a WTO member wishes to deviate from an existing international standard, measures have to be based on a risk assessment. A risk assessment is defined as the evaluation of the likelihood of entry, establishment or spread of a pest or disease within the territory of an importing member according to the sanitary or phytosanitary measures which might be applied, and of the associated potential biological and economic circumstances. Risk assessments must take into account risk assessment techniques developed by the relevant international organizations. Risk assessments also have to take into account available scientific evidence; relevant processes and production methods; prevalence of specific diseases or pests; existence of pest- or disease-free areas; relevant ecological and environmental conditions; and quarantine or other treatment.

In situations where relevant scientific evidence is insufficient to carry out a risk assessment, the SPS Agreement allows members to adopt provisional sanitary and phytosanitary measures on the basis of the available pertinent information, including that from relevant international organizations and from measures applied by other members. When they adopt such provisional measures, members have to try to obtain additional information to allow them to carry out a risk assessment, and review the provisional measure within a reasonable period of time.

5.2. Pests, diseases, disease-carrying organisms or disease-causing organisms

Sanitary and phytosanitary measures may be relevant to components, organisms and products resulting from synthetic biology if they result in pests, diseases, disease-carrying organisms or disease-causing organisms with negative impacts on human, animal or plant life or health. The SPS Agreement, however, does not define "diseases, disease-carrying organisms or disease-causing organisms", nor "pests". A footnote clarifies that, for the purpose of the definitions of the SPS Agreement (Article 1, paragraph 2 in conjunction with Annex A SPS Agreement), "pests" include weeds. The WTO Panel on the *Biotech* dispute,[98] in its report, understood pests as an animal or plant which is destructive, or causes harm to the health of other animals, plants or humans, or other harm, or a troublesome or annoying animal or plant (WTO Dispute Settlement Report, Biotech, 2006). As has been discussed in sections 2.3.1 and 3.1.1 above, organisms resulting from synthetic biology techniques are expected to constitute "living modified organisms" under the Convention on Biological Diversity and its Cartagena Protocol. As the Biotech dispute was concerned with genetically modified plants, the panel report of this dispute may help an understanding of how the provisions of the SPS Agreement may apply to organisms and products resulting from synthetic biology techniques.

The Panel applied a wide interpretation of the term plant life or health. It held that "the potential effects of genetically modified plants relate to situations where genetically modified plants grow where they are undesired". In such situations, due to a potential competitive advantage, persistence and invasiveness, genetically modified plants may crowd out or eliminate other plants. Competitive pressure

98 The conclusions and recommendations contained in a dispute settlement report become only binding upon the parties to the dispute. Subsequently established panels are not bound by interpretations contained in previous reports.

from genetically modified plants may also affect the genetic diversity of remaining plant populations, putting at risk the survival of certain plant species. As these potential effects of genetically modified plants impact negatively on the ability of other plants to exist and survive in the affected area, (…) they can be considered to cause harm to the "life or health" of other plants" (WTO Dispute Settlement Report, Biotech, 2006).

With regard to the scope of what is considered as an "animal or plant" in its definition of a pest, the Panel noted that the International Standard for Phytosanitary Measures (ISPM) No. 11 of the International Plant Protection Convention states that a living modified organism may be deemed to be a "pest" if the living modified organism is associated with "adverse effects of gene flow or gene transfer including, for example (…) transfer of pesticide or pest resistance genes to compatible species". The Panel noted further that Annex 3 of ISPM No. 11 "does not suggest that the transgene should or could be viewed as a "pest" in its own right" (WTO Dispute Settlement Report, Biotech, 2006).

In addition, the Panel stated that "even if a genetically modified plant which cross-breeds with other plants were not itself viewed as a "pest", the cross-breeds could be regarded as "pests" for the purposes of Annex A(1) [of the SPS Agreement], to the extent they have undesired introduced traits (such as herbicide or insect resistance) and harm animal, plant or human life or health or result in other damage". It also noted that "even if a genetically modified plant to which insect populations develop resistance were not viewed as a "pest", (…) the resistant target or non-target organisms (i.e., the resistant insects) could be regarded as "pests" within the meaning of Annex A(1) [of the SPS Agreement], inasmuch as they present a risk to animal, plant or human life or health or result in other damage" and further that "to the extent that genetically modified plants may result in changes in animal or plant populations (including in target organism populations), this may increase or decrease the food available for particular non-target animal populations and thus enhance, or detract from, the fitness and health of these animal populations, which in turn may have a deleterious effect on the life or health of plants, e.g., by affecting their ability to reproduce, etc. These effects would thus impact on the genetic diversity of an ecosystem, including populations of species, (…) by causing harm to the life or health" (WTO Dispute Settlement Report, Biotech, 2006).

With regard to the definition of "diseases, disease-carrying organisms or disease-causing organisms", the Panel observed that the common (dictionary) definition of the term "disease" as it appears in Annex A(1)(a) of the SPS Agreement is "a disorder of structure or function in an animal or plant of such a degree as to produce or threaten to produce detectable illness or disorder". Regarding the term "disease-carrying organisms" and "disease-causing organisms" the Panel noted the definitions of the World Health Organization, which defines a disease-carrying organism as a "vector" and a disease-causing organism as a "pathogen". It stated that European Union Directives 90/220 and 2001/18 thus seek to prevent genetically modified plants from introducing or spreading diseases, and from altering the susceptibility of animals or plants to pathogens, which might facilitate the introduction or spread of disease-causing organisms (that is, pathogens) or create new disease-carrying organisms (vectors), and that, in light of this, the Directives can be considered as sanitary or phytosanitary measures under Annex A, paragraph 1 (a) of the SPS Agreement (WTO Dispute Settlement Report, Biotech, 2006).

These explanations show that organisms resulting from synthetic biology could, depending on the specific case, be considered as causing risks to animal or plant life or health arising from the entry, establishment or spread of pests, diseases, disease-carrying organisms or disease-causing organisms. As discussed in section 6 of Part I of this document on potential impacts, organisms and products resulting from synthetic biology may be intentionally or unintentionally released to the environment, leading to biosafety concerns. Depending on the circumstances, they could be considered to pose risks to animal or plant life or health, through ecosystem-level impacts or the transfer of synthetic DNA.[99] WTO members may take measures to address these risks in accordance with the requirements summarized in the previous section.

5.3. Additives, contaminants, toxins or disease-causing organisms in foods, beverages or feedstuffs

Components, organisms and products resulting from synthetic biology could arguably also be addressed through measures to protect human or animal life or health within the territory of a WTO Member from risks arising from additives, contaminants, toxins or disease-causing organisms in foods, beverages or feedstuffs (Annex A, paragraph 1 b).

The WTO Panel on the *Biotech* dispute also provided guidance for the case of genetically modified organisms. It held that "a genetically modified crop

99 *Potential health applications of synthetic biology are discussed in section 11 of Part I of this document on potential impacts.*

grown for the explicit purpose of providing food to animals, and in particular to farmed animals, would qualify as a "feedstuff". A genetically modified crop that has been grown for a different purpose, but is eaten by animals, including wild fauna, can be considered to be a "food" for that animal. This would include, for example, pollen of the genetically modified crop which is consumed by insects and genetically modified plants consumed by non-target insects, deer, rabbits or other wild fauna." The panel stated that "genetically modified seeds used for sowing purposes could also be considered animal "food", for instance if these seeds are spilled next to a field or on a farm and are subsequently eaten by birds, etc."

With regard to the definition of "additives" the Panel held that "genes, intentionally added for a technological purpose to genetically modified plants that are eaten or being used as an input into processed foods, can be considered "additives in foods" within the meaning of Annex A(1)(b). This should not be construed to mean, however, that all genes of a plant that is eaten or being used as input into processed foods could be classified as "additives" (WTO Dispute Settlement Report, Biotech, 2006).

The Panel stated further that "contaminants" must be interpreted so as to have a meaning that differs from the meaning of the term "additive" and that the decisive element in this regard is that the presence of the substance which is said to "infect or pollute" is unintentional. Genes intentionally added to genetically modified plants that are eaten or used as inputs into processed foods would not be "contaminants" in and of themselves. Also, substances such as proteins which are produced by genetically modified plants, and which are intended, should not be considered to be "contaminants". However, proteins produced through the unintended expression of modified genes in agricultural crops may be considered "contaminants" within the meaning of Annex A(1)(b) if these proteins "infect or pollute" (WTO Dispute Settlement Report, Biotech, 2006).

With regards to the definition of "toxin" the Panel stated that "a poisonous substance which is produced during the metabolism or growth of a genetically modified crop could qualify as a "toxin" within the meaning of Annex A(1)(b)." It noted that "for an SPS measure to be covered by Annex A(1)(b), the toxin which gives rise to risks for human or animal life or health would have to be present in "foods, beverages or feedstuffs"," but recalled at the same time that "a genetically modified plant which is grown in a field may be eaten as food by wild fauna." The Panel also stated that food allergens at issue in the dispute can be considered as "toxins". The Panel did not give any guidance as to the interpretation of the term "disease-causing organisms" (WTO Dispute Settlement Report, Biotech, 2006).

Case-by-case assessments would be necessary to determine whether any components, organisms or products of synthetic biology would be covered by Annex A(1)(b). At this point, applications of synthetic biology do not seem to be focusing on developing food crops for human use, but the potential for synthetic biology to enhance agricultural efficiency and lessen its environmental impacts is often invoked (see section 5.4 of Part I of this document on potential impacts). Where organisms resulting from synthetic biology could be accessed by wild fauna, they may qualify as "feedstuffs." For example, outdoor ponds of algae resulting from synthetic biology techniques may be accessible to wildlife (Snow & Smith 2012). Whether any components, organisms or products of synthetic biology that qualified as a food, beverage, or feedstuff would also be considered an additive, contaminant or toxin would, again, require a case-by-case assessment, taking into account the intended expressions of synthetic genetic sequences.

6. THE INTERNATIONAL PLANT PROTECTION CONVENTION (IPPC)

The International Plant Protection Convention (IPPC) promotes action to protect plants and plant products from the spread of pests, and sets out measures to control plant pests (see Article I IPPC). The latest version of the Convention entered into force in 2005; it has 181 Parties.

6.1. Overview of main provisions

The main provisions of the IPPC include the requirement for each Party to establish a national plant protection organization with a specified mandate (Article IV IPPC) and to make arrangements for the issuance of phytosanitary certificates (Article V IPPC). Further, Parties may require, under certain conditions, phytosanitary measures for quarantine pests and regulated non-quarantine pests (Article VI IPPC). Parties also have sovereign authority to regulate, in accordance with applicable international agreements, the entry of plants and plant products and other regulated articles with the aim of preventing

the introduction and/or spread of regulated pests into their territories (Article VII, paragraph 1 IPPC). To this end, Parties may:

- Prescribe and adopt phytosanitary measures concerning the importation of plants, plant products and other regulated articles, including, for example, inspection, prohibition on importation, and treatment;
- Refuse entry or detain, or require treatment, destruction or removal from the territory of the contracting party, of plants, plant products and other regulated articles or consignments thereof that do not comply with the phytosanitary measures prescribed or adopted under subparagraph (a);
- Prohibit or restrict the movement of regulated pests into their territories;
- Prohibit or restrict the movement of biological control agents and other organisms of phytosanitary concern claimed to be beneficial into their territories.

In order to minimize interference with international trade, Parties have to undertake these activities in conformity with a set of requirements provided in Article VII, paragraph 2.

In Article X, Parties agree to cooperate in the development of international standards which they should take into account when undertaking activities related to the Convention. In accordance with these provisions, the international framework for plant protection includes International Standards for Phytosanitary Measures (ISPMs). The adopted standards under the IPPC[100] provide guidance to its Parties on Phytosanitary Principles for the Protection of Plants, and the application of phytosanitary measures in international trade, with specific standards covering not only pest risk analysis but also import and export systems, post-border controls and surveillance and reporting on pests and diseases.

6.2. Phytosanitary measures

The International Plant Protection Convention defines phytosanitary measures in Article 2 as any legislation, regulation or official procedure having the purpose to prevent the introduction and/or spread of pests. Pests, in turn, are defined as any species, strain or biotype of plant, animal or pathogenic agent injurious to plants or plant products. Plants are living plants and parts thereof, including seeds and germplasm. Plant products are defined as unmanufactured material of plant origin (including grain) and those manufactured products that, by their nature or that of their processing, may create a risk for the introduction and spread of pests.

While the primary focus of the International Plant Protection Convention is on plants and plant products moving in international trade, it also covers research materials; biological control organisms; germplasm banks; containment facilities and anything else that can act as vectors for the spread of plant pests (e.g. containers, packaging materials, soil, vehicles, vessels and machinery). Regulated articles comprise any plant, plant product, storage place, packaging, conveyance, container, soil and any other organism, object or material capable of harbouring or spreading pests, deemed to require phytosanitary measures, particularly where international transportation is involved (see also Article 1, paragraph 3 IPCC).

Annex 3 of ISPM No. 11 clarifies further for the case of living modified organisms that for phytosanitary risks related to gene flow, the living modified organism is acting more as a potential vector or pathway for introduction of a genetic construct of phytosanitary concern rather than as a pest in and of itself. Therefore, the term "pest" should be understood to include the potential of a living modified organism to act as a vector or pathway for introduction of a gene presenting a potential phytosanitary risk. Annex 3 of ISPM No. 11 contains a list of potential phytosanitary risks from living modified organisms. All these risks may apply, to varying degrees, to components, organisms and products resulting from synthetic biology.

Other ISPMs which have been identified as relevant to living modified organisms (Convention on Biological Diversity 2012), and therefore may in some cases be relevant to components, organisms and products resulting from synthetic biology, include:

- ISPM No. 12: Guidelines for phytosanitary certificates (2001)
- ISPM No. 7: Export certification systems (1997)
- ISPM No. 3: Guidelines for the export, shipment, import and release of biological control agents and other beneficial organisms (2005)
- ISPM No. 20: Guidelines for a phytosanitary import regulatory system (2004)
- ISPM No. 23: Guidelines for inspection (2005).

100 *Available at: www.ippc.int/core-activities/standards-setting/ispms#block-agenda-items-list.*

7. THE WORLD ORGANISATION FOR ANIMAL HEALTH

The World Organisation for Animal Health was founded in 1924 as the Office International des epizooties (OIE) to provide international cooperation and coordination against the spread of animal diseases. Ninety years later, the core mandate of the organisation has been expanded to become the improvement of animal health world-wide.

The OIE standards, recognized by the SPS Agreement as the international standards for animal health including zoonosis, are published as the OIE Animal Health Codes (Terrestrial Animal Health Code and Aquatic Animal Health Code) and the OIE Manuals (Manual of Diagnostic Tests and Vaccines for Terrestrial Animals and Manual of Diagnostic Tests for Aquatic Animals). These international standards cover a wide range of animal health and veterinary public health matters. They include the obligation to issue notifications, undertake import risk analyses, surveillance, disease prevention and control measures, establish trade requirements for animals and animal products, and require the use of diagnostic tests and vaccines and others.

A sanitary measure under the OIE means a measure, such as those described in various chapters of the Terrestrial Code, destined to protect animal or human health or life within the territory of the Member Country from risks arising from the entry, establishment and/or spread of a hazard. A hazard is defined in the Terrestrial Code as a biological, chemical or physical agent in, or a condition of, an animal or animal product with the potential to cause an adverse health effect.

As this definition is quite broad, components, organisms and products resulting from synthetic biology techniques could potentially fall thereunder. As mentioned previously, although current applications of synthetic biology are mostly in micro-organisms, synthetic biology research in mammalian and other eukaryotic cells is making rapid progress. OIE standards may be relevant to synthetic biology techniques both in terms of synthetic biology helping to develop vaccines and therapies for animal diseases and in terms of possibly producing adverse health effects.

Source: Macroscopic Solutions, LLC

8. CODEX ALIMENTARIUS

The Codex Alimentarius Commission is a joint initiative of the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) that was set up to establish international standards on foods.[101]

The Codex Alimentarius is a collection of internationally adopted food standards presented in a uniform manner. These are developed in order to attempt to ensure that products meet internationally accepted minimum quality levels, are safe, and do not present a health hazard. Standards are prescribed for individual foods and food groups, and general standards have also been adopted. In addition to specific standards, the Codex also includes "related texts". Related texts include advisory instruments: statements of principle, codes of practice, guidelines and codes of technological practice. Some of these instruments apply to food and food products that have been derived from synthetic biology techniques.

Standards adopted by the Codex Alimentarius Commission are not legally binding on Codex member States. Countries and organizations that are members of the World Trade Organization (WTO), however, have a general obligation under the SPS Agreement to base their sanitary or phytosanitary measures on international standards, guidelines or recommendations, where they exist, for the purpose of harmonizing these measures on as wide a basis as possible (Article 3, paragraph 1 SPS Agreement). Annex A to the SPS Agreement defines the term 'international standards, guidelines and recommendations' to mean, in the context of food safety, the standards, guidelines and recommendations established by the Codex Alimentarius Commission (paragraph 3(a)).

Documents relevant to components, organisms and products resulting from synthetic biology include, for example:[102]

- Principles for the Risk Analysis of Foods Derived from Modern Biotechnology;
- Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants" and its annex on "Food Safety Assessment of Foods Derived from Recombinant-DNA Plants Modified for Nutritional or Health Benefits;
- Guideline for the Conduct of Food Safety Assessment of Foods Produced using Recombinant-DNA Microorganisms;
- Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals; and the
- Annex on Food Safety Assessment in Situations of Low-level Presence of Recombinant-DNA Plant Material in Food.

These standards may apply if components, organisms and products resulting from synthetic biology are used as foods. The term "modern biotechnology" has the same definition under the Codex Alimentarius and the Cartagena Protocol. For an analysis see therefore sections 2.3 and 3.1.3 above.

101 *For an introduction to the Codex Alimentarius see http://www.codexalimentarius.org/about-codex/en/.*

102 *These documents are available online at www.codexalimentarius.org/standards/list-of-standards/.*

Sources: Macroscopic Solutions, LLC

Source: iGEM Foundation

D. TREATIES ADDRESSING ACCESS TO GENETIC RESOURCES, BENEFIT-SHARING FROM THEIR UTILIZATION, TECHNOLOGY TRANSFER AND INTELLECTUAL PROPERTY RIGHTS THAT COULD BE RELEVANT TO THE APPLICATION OF SYNTHETIC BIOLOGY TECHNIQUES

Besides the Nagoya Protocol, the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) also addresses aspects of the fair and equitable sharing of benefits arising out of the use of specific genetic resources. The Agreement on Trade Related Aspects of Intellectual Property Rights and the International Convention for the Protection of New Varieties of Plants may provide for certain intellectual property rights associated with components, organisms and products resulting from synthetic biology techniques and are therefore discussed below.[103]

9. CONVENTION ON BIOLOGICAL DIVERSITY

Depending on the scope of synthetic biology's definition, the following Convention provisions could be relevant with regard to access to genetic resources and benefit-sharing from their utilization, as well as transfer of technologies:

9.1. Access and Benefit-sharing of Genetic Resources (Article 15)

9.1.1. Genetic resources for their use in synthetic biology[104]

Article 15, paragraph 1 of the Convention recognizes the sovereign rights of States over their natural resources, and provides that the authority to determine access to genetic resources rests with national governments and is subject to national legislation. Article 15 may be particularly relevant to synthetic biology with regard to the access to genetic resources for use in synthetic biology processes.

While the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization details much more precise obligations in relation to access and benefit-sharing for its Parties, Article 15 of the Convention continues to apply to all Parties of the Convention.[105]

Article 15 includes the provisions that Parties shall endeavour to create conditions to facilitate access to genetic resources for environmentally sound

103 *A treaty which may be relevant for the specific procedure of patent application is the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The Budapest Treaty eliminates the need to deposit microorganisms in each country where patent protection is sought. This treaty is not further discussed in the present dcoument as procedural requirements lie beyond its scope.*

104 *It should be noted that this document is made available for the information of Parties to the Convention and is not intended to affect the rights and obligations of Parties to the Convention or its Protocols.*

105 *Section 3.2 on the Nagoya Protocol discusses a number of questions raised by synthetic biology techniques that could also be applicable to Article 15.*

Source: Macroscopic Solutions, LLC

uses by other Contracting Parties (paragraph 2); that granted access shall be on mutually agreed terms (paragraph 4) and subject to prior informed consent, unless otherwise determined by the Party providing the genetic resources (paragraph 5); and that "Parties shall take legislative, administrative or policy measures … with the aim of sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources with the Contracting Party providing such resources" (paragraph 7).

In the cases where synthetic biology utilizes genetic resources and requires access to those resources, the access requirements of the Convention would, in general, apply and thus require prior informed consent (unless otherwise determined) and the negotiation of mutually agreed terms.

However, there are cases where it is not clear that the material accessed for its use in synthetic biology can be considered "genetic resources" or "genetic material" in accordance with the definitions contained in Article 2 of the Convention. The Convention defines "genetic resources" as genetic material of actual or potential value. Additionally, "genetic material" is defined as any material of plant, animal, microbial or other origin containing functional units of heredity.

Therefore, "genetic material" includes material from any origin so long as it contains "functional units of heredity". Functional units of heredity are not defined in the text of the Convention. Schei and Tvedt (2010) argue that because the word "functional" introduces a dynamic element, the term "genetic material" can be interpreted in line with contemporary knowledge and technology. When the Convention was negotiated, the general understanding was that functional units of heredity distinguished genes from "junk" DNA. Today, however, scientific understandings of heredity have changed dramatically; junk DNA is no longer considered "junky," and some suggest that functional units of heredity may need to be interpreted beyond the gene itself (Schei and Tvedt 2010).

As said above, the Convention defines "genetic resources" as genetic material of actual or potential value. "Value" within the context of the Convention includes not just economic value, but also ecological, genetic, social, scientific, educational, cultural, recreational and aesthetic values (Preamble). Schei and Tvedt (2010) argue that because the definition refers to both types of value – actual and potential – it encompasses the state of art of technology as well as dynamic future realizations of value. Synthetic biology tools and techniques are aiding researchers in discovering new aspects of value in materials (Laird and Wynberg 2012). Synthetic biology is opening up new ways to capture increased value from genetic materials, and thus may affect Parties' interpretations of the definitions of "genetic resources" and "genetic material" as contained in the Convention and, by reference, the Nagoya Protocol.

For example, components used in synthetic biology include virtual/digital information on functional units of heredity, such as specific DNA sequences. As noted previously, analysts have noted a growing trend in research away from physical transfers of biological material and towards electronic transfers of information, within biotechnology more broadly as well as specifically with the use of synthetic biology tools and techniques (Oldham 2004; Schei and Tvedt 2010; Laird and Wynberg 2012; ICSWGSB 2011). Researchers are utilizing information about the genetic composition – for example, the DNA sequences - instead of the physical genetic resource.

There could be differing interpretations of whether virtual/digital information about genes and other genetic elements can be considered "genetic resources" or "genetic material" in accordance with the definitions contained in the Convention. In an analysis commissioned by the Executive Secretary, Schei and Tvedt (2010) argue that the informational aspect of functional units of heredity is part of a dynamic understanding of the definition. Schei and Tvedt note that the "value" of functional units of heredity can be captured in its genetic structure and in the information of the nucleotide sequence (Schei and Tvedt 2010). They appear to suggest that the standing definition of the Convention of genetic resources could be interpreted to include digital DNA sequences.

Others interpret the matter differently. For example, the ICSWGSB suggests that the Conference of the Parties to invite Parties to the Nagoya Protocol to consider extending agreements on access and benefit-sharing to cover digital sequences (ICSWGSB 2011) because it considers the Nagoya Protocol as not covering digital sequences and products derived from natural sequences using synthetic biology.

9.1.2 Genetic resources originating from synthetic biology

Another open question is whether the components, organisms and products resulting from synthetic biology can be considered "genetic resources" under the Convention.

For example, there are different areas of synthetic biology research that may raise different considerations regarding whether they constitute

Source: Macroscopic Solutions, LLC

genetic resources within the definition of the Convention:

- **DNA-based parts and devices, synthetic metabolic pathway engineering, and genome-level engineering** – These areas of research involve designing and synthesizing stretches of DNA, RNA, and whole genomes. The organisms resulting from these synthetic biology techniques contain DNA. However, the products these organisms are designed to create, such as pharmaceutical molecules and fuel, generally do not contain DNA.
- **Protocell construction** – Protocell research aims to create the simplest possible components to sustain reproduction, self-maintenance and evolution (Lam *et al*. 2009; Sole *et al*. 2007). Protocell designs usually contain some kind of information-carrying molecule; these could possibly be understood to functionally operate as "units of heredity." However, some protocell research is attempting to develop cells without the ability to evolve or replicate (PCSBI 2010; Sole *et al*. 2007; Schmidt *et al*. 2009). Depending on the meaning of functional units of heredity, such cells may not fall within the definition of "genetic material."
- **Xenobiology** – As with protocells, research in this area is far from commercialization or use (Sutherland *et al*. 2013; Joyce 2012). This research focuses on altering the basic form of nucleic and amino acids, for example by creating nucleic acids with novel bases or novel backbones. Whether this would be considered "genetic material" depends on whether XNA, xDNA, and other modified forms of information-carrying molecules would be considered to operate as functional units of heredity. One of the hoped-for results of this research is orthogonal organisms whose altered information molecules would lead to semantic containment (see section 7.2 of Part I of this document on potential impacts). These organisms may still be able to reproduce themselves, however, so they may be understood to contain functional units of heredity.

The consideration of the components, organisms and products resulting from synthetic biology as genetic resources within the context of the Convention would raise some questions regarding the application of the principle of state sovereignty over genetic resources and access and benefit-sharing obligations as well as the application of the Convention's provisions regarding the conservation and sustainable use of biodiversity.

9.2. Technology Transfer and Cooperation (Articles 16-19)

The Convention has established a programme of work on technology transfer and cooperation based on Articles 16 to 19 (see decision VII/29). Article 16, paragraph 1 provides that each Party will undertake "to provide and/or facilitate access for and transfer to other Contracting Parties of technologies that are relevant to the conservation and sustainable use of biological diversity or make use of genetic resources and do not cause significant damage to the environment". Article 16 explicitly includes "biotechnology" in the provisions on access to and transfer of technology (Article 16, paragraph 1). As discussed above in sections 2.3 and 3.1.3, technologies associated with synthetic biology may, on a case-by-case basis, fall under the definition of biotechnology.

Technologies associated with synthetic biology may fulfill both criteria set out in Article 16, paragraph 1: (i) be of relevance to conservation and sustainable use of biodiversity, and (ii) use genetic resources and not cause significant damage to the environment. Case-by-case assessments would be needed to determine whether specific technologies apply. Generally speaking, some areas of synthetic biology research do aim to produce applications relevant to conservation and sustainable use, such as de-extinction and the creation of microbes for pollution remediation (see section 5.2 of Part I of this document on potential impacts). Such areas of research are mostly considered to still be far from application or commercialization. Other areas, such as engineering microbes to produce molecules that are otherwise naturally-occurring for use as flavors and fragrances, are close to commercialization, and may be relevant to conservation and sustainable use depending on the natural product being displaced (see section 5.5 of Part I of this document on potential impacts). As discussed above, much of synthetic biology research could be considered to "make use of genetic resources." Whether or not specific synthetic biology technologies cause significant damage to the environment would require an impact assessment.

Developing countries are to be provided "fair and most favorable terms" to access to and transfer of technologies (Article 16, paragraph 2) that "are relevant to the conservation and sustainable use of biological diversity or make use of genetic resources and do not cause significant damage to the environment" (Article 16, paragraph 1). Article 19 also specifically addresses developing countries, holding that Parties "shall take all practicable measures to promote and advance priority access on a fair and equitable basis by Contracting Parties,

especially developing countries, to the results and benefits arising from biotechnologies based upon genetic resources provided by those Contracting Parties" (Article 19, paragraph 2), and that they shall "provide for the effective participation in biotechnological research activities by those Contracting Parties, especially developing countries, which provide the genetic resources for such research, and where feasible in Contracting Parties" (Article 19, paragraph 1).

A 2012 article in *PLoS ONE* determined the global landscape of synthetic biology research, based on the location of authors in *Web of Science* publications (Oldham *et al*. 2012). While the majority of synthetic biology publications come out of the USA, followed by the UK, Germany, France and Switzerland, other countries are on the map. The authors specifically point out the presence of emerging major economies, such as China, Brazil, and India, along with Mexico, Argentina, South Africa and Singapore (Oldham *et al*. 2012). Thus, synthetic biology research is occurring in some of the "mega-diverse" countries.

10. NAGOYA PROTOCOL ON ACCESS TO GENETIC RESOURCES AND THE FAIR AND EQUITABLE SHARING OF BENEFITS ARISING FROM THEIR UTILIZATION TO THE CONVENTION ON BIOLOGICAL DIVERSITY

Depending on the scope of synthetic biology's definition, the following Nagoya Protocol provisions could be relevant with regard to access to genetic resources and benefit-sharing from their utilization.

The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (the Nagoya Protocol) was adopted on 29 October 2010 and will enter into force on 12 October 2014.[106]

The Nagoya Protocol aims to support the implementation of the third objective of the Convention and builds on its provisions, including Article 15, by setting out core obligations for Parties in relation to access to genetic resources and traditional knowledge associated with genetic resources, benefit-sharing and compliance.

Article 2 of the Nagoya Protocol provides that the definitions of the Convention apply to the Protocol, and consequently, discussions on the definitions of "genetic resources" and "genetic material" included in section 3.1.1 are also relevant for this chapter.

The following examines additional issues relevant to the application of the Nagoya Protocol to uses of synthetic biology.

10.1. Synthetic biology and the "utilization of genetic resources"

Article 2 of the Nagoya Protocol addresses the use of terms in the Protocol. It provides that the terms defined in Articles 2 of the Convention also apply to the Protocol. It defines "utilization of genetic resources" as conducting research and development on the genetic and/or biochemical composition of genetic resources, including through the application of biotechnology. Furthermore, "biotechnology" as defined in Article 2 of both the Convention and the Protocol means any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use. These definitions can help to clarify the issue of scope of access and benefit-sharing obligations.

The Nagoya Protocol adds also the definition of "derivative" as a naturally occurring biochemical compound resulting from the genetic expression or metabolism of biological or genetic resources, even if it does not contain functional units of heredity. Synthetic biology applications may be a way of "utilizing" genetic resources as defined in the Nagoya Protocol.

The definitions can also help to determine which activities related to synthetic biology would be within the scope of the Nagoya Protocol. For example, as previously discussed (section 2.3.3 above), a major focus of current synthetic biology research is on designing organisms that will use biomass as feedstock to produce fuels, chemicals, and pharmaceuticals (PCSBI 2010). Synthetic biology companies such as Amyris are locating their facilities in Brazil in order to be near sources of sugarcane for use as feedstock for such micro-organisms. If used *solely* as a feedstock, this use of sugarcane would likely not fall within the "utilization of genetic resources." However, if research was conducted on the sugarcane to determine if it was an appropriate feedstock or if it could be transformed to be more suitable, this research could be interpreted as

106 *See http://www.cbd.int/abs/nagoya-protocol/signatories/default.shtml.*

"utilization" within the terms of the Nagoya Protocol, and access to the sugarcane for this purpose would be subject to applicable access obligations of the Nagoya Protocol and domestic legislation or regulatory requirements implementing these obligations.

10.2. Benefit-sharing and the degree of modification of genetic resources

Synthetic biology techniques provide ways to modify naturally occurring genetic resources so that they better serve specific purposes. One method is by directed evolution, such as the Wyss Institute's MAGE machine which can generate billions of different mutant genomes per day, performing up to 50 different genome alterations at nearly the same time, using synthetic DNA (Wang *et al*. 2009).[107] Another method is to use computers to design a stretch of DNA so that it is "codon-optimized" and the gene more efficiently expresses the characteristics in the target organism as desired by the researchers (Endy 2005) (see also sections 2 and 3 of Part I of this document on potential impacts).

The use of these synthetic biology techniques raises questions as regards to until what extent the results of modifications of a natural genetic resource continue to be subject to the benefit-sharing obligations. Article 5, paragraph 1 of the Nagoya Protocol requires that benefits arising from the utilization of genetic resources "as well as subsequent applications and commercialization" shall be shared in a fair and equitable way. It also provides that "such sharing shall be upon mutually agreed terms". According to Greiber, this is meant to extend benefit-sharing to processes and products developed along the value chain (Greiber *et al*. 2012).

The ICSWGSB interprets the Nagoya Protocol as not covering "products derived from natural sequences using synthetic biology tools such as directed evolution techniques," and calls for Parties to the Protocol to include them (ICSWGSB 2011). In comments to this draft document, one organization similarly interprets the Nagoya Protocol as not covering such products, and believes that expansion of the Nagoya Protocol to such products would go "much further down the value chain than is appropriate."

National implementation and the negotiation of mutually agreed terms can assist parties to an access and benefit-sharing agreement to clarify until which extent of the value chain the obligations to share benefits would continue to apply to components, organisms and products resulting from synthetic biology.

10.3. Derivatives and synthetic biology[108]

The Nagoya Protocol in its Article 2 defines a "derivative" as a naturally occurring biochemical compound resulting from the genetic expression or metabolism of biological or genetic resources, even if it does not contain functional units of heredity.

Synthetic biology raises a number of questions in relation to the application of the Nagoya Protocol to derivatives. For instance, whether or not biochemical compounds produced by synthesized organisms could be considered a "derivative" as defined by the Protocol.

For example, a valuable natural derivative is isoprene, the major molecule of rubber. The enzyme isoprene synthase has only been found in plants – namely, *Hevea brasiliensis*, the rubber tree – but plant genes are not efficiently expressed in microorganisms (Erickson *et al*. 2011). The Genencor Division of Danisco and Goodyear Tire and Rubber Company have partnered in research to develop "BioIsoprene," using synthetic biology in the "construction of a gene that encodes the same amino acid sequence as the plant enzyme but is optimized for expression in engineered microorganisms" (Erickson *et al*. 2011).

An initial question is whether genetic resources from *H. brasiliensis* were actually accessed and "utilized" in the context of the Protocol. A separate question might be whether access to derivatives of organisms resulting from synthetic biology techniques – such as isoprene – would also be covered by the Nagoya Protocol (see similar discussion on access to genetic resources originating from synthetic biology in section 9.1.1 above)

There are different interpretations regarding how the Nagoya Protocol applies to derivatives. It could be argued that the benefit-sharing obligations apply to derivatives through linkages with the definitions of utilization of genetic resources and biotechnology (Article 2 Nagoya Protocol, see Greiber *et al*. 2012; Nijar 2011). Another possible interpretation is that the operative provisions of the Protocol apply only to genetic resources, and not to derivatives.[109]

107 *See http://wyss.harvard.edu/viewpage/330/, accessed on 23 March 2013.*

108 *It should be noted that this document is made available for the information of Parties to the Convention and is not intended to affect the rights and obligations of Parties to the Convention or its Protocols.*

109 *See Nijar (2011) for descriptions of the arguments for differing interpretations of the role of derivatives in the Nagoya Protocol.*

National implementation of the Nagoya Protocol can assist in further clarifying the definition of "utilization" as well as the scope of access and benefit-sharing requirements in relation to derivatives. The negotiation of mutually agreed terms can assist parties to access and benefit-sharing agreements to clarify until which extent of the value chain the obligations to share benefits would continue to apply to components, organisms and products resulting from synthetic biology, including derivatives and their subsequent applications.

11. INTERNATIONAL TREATY ON PLANT GENETIC RESOURCES FOR FOOD AND AGRICULTURE

The International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) entered into force in 2004 and has 131 Parties as of 2014. In adopting the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity, the Conference of the Parties to the Convention on Biological Diversity recognized the ITPGRFA as one of the "complementary instruments" that constitute the International Regime on access and benefit-sharing and recognized that the objectives of the ITPGRFA are the conservation and sustainable use of plant genetic resources for food and agriculture and the fair and equitable sharing of the benefits arising out of their use, in harmony with the Convention on Biological Diversity, for sustainable agriculture and food security. Depending on the scope of synthetic biology's definition, the following provisions could be relevant with regard to access to genetic resources and benefit-sharing from their utilization.

11.1. Overview of main provisions

Article 2 of the ITPGRFA defines plant genetic resources for food and agriculture as any genetic material of plant origin of actual or potential value for food and agriculture. "Genetic material" is defined as any material of plant origin, including reproductive and vegetative propagating material, containing functional units of heredity. These definitions are similar to those of the Convention, which defines genetic resources as genetic material of actual or potential value, and genetic material as any material of plant, animal, microbial or other origin containing functional units of heredity (Article 2). For an analysis see therefore also section 9.1.1 above. The main difference between the two treaties is that the definitions under the ITPGRFA only refer to material of plant origin. However, plant genetic resources are the raw material and indispensable for crop genetic improvement.

As discussed in section 5.4 of Part I of this document on potential impacts, agricultural applications of synthetic biology are a focus of current research, as is the production of specialized plant feedstocks for bioenergy purposes. According to the IUCN explanatory guide to the ITPGRFA, the treaty text is ambiguous in whether functional units of heredity are in themselves PGRFA or are components of PGRFA (Moore & Tymowski 2005). Thus, if synthetic biology research is based upon DNA sequences of PGRFA, it may be a matter of interpretation whether the research is utilizing PGRFA.

According to Article 5 of the ITPGRFA, Parties are required, subject to certain qualifiers, to promote an integrated approach to the exploration, conservation and sustainable use of plant genetic resources for food and agriculture which includes, in particular, the following activities which may be relevant for synthetic biology techniques:

- Promote the collection of plant genetic resources for food and agriculture and relevant associated information on those plant genetic resources that are under threat or are of potential use;
- Promote *in situ* conservation of wild crop relatives and wild plants for food production, including in protected areas, by supporting, inter alia, the efforts of indigenous and local communities;
- Cooperate to promote the development of an efficient and sustainable system of ex situ conservation, giving due attention to the need for adequate documentation, characterization, regeneration and evaluation, and promote the development and transfer of appropriate technologies for this purpose with a view to improving the sustainable use of plant genetic resources for food and agriculture; and
- Monitor the maintenance of the viability, degree of variation, and the genetic integrity of collections of plant genetic resources for food and agriculture; and
- Take steps to minimize or, if possible, eliminate threats to plant genetic resources for food and agriculture.

These obligations are relevant for synthetic biology in that they support the availability of a broad resource base upon which synthetic biology techniques can draw.

11.2. Multilateral system of access and benefit-sharing

In Article 10, paragraph 2 of the ITPGRFA, Parties established a multilateral system to facilitate access to plant genetic resources for food and agriculture, and to share, in a fair and equitable way, the benefits arising from the utilization of these resources, on a complementary and mutually reinforcing basis. The Multilateral System applies to the plant genetic resources for food and agriculture listed in Annex I to the treaty, a pool of 64 food and forage crops, established according to criteria of food security and interdependence. Some of these Annex I crops are the focus of synthetic biology research. One example is the modification of maize to be a more efficient biofuel feedstock (see section 5.1 of Part I of this document on potential impacts). Also, some synthetic biology research is focused on modifying micro-organisms to produce substances that would substitute for Annex I crops, such as lauric acids that are currently produced in part from coconuts (see section 10 of Part I of this document on potential impacts)

Article 12 requires Parties to provide facilitated access to plant genetic resources for food and agriculture to other Parties, including to legal and natural persons under their jurisdiction. This access is to be granted pursuant to a standard material transfer agreement (MTA) through the Multilateral System under certain conditions, including:

- Access shall be provided solely for the purpose of utilization and conservation for research, breeding and training for food and agriculture, provided that such purpose does not include chemical, pharmaceutical and/or other non-food/feed industrial uses.
- Recipients shall not claim any intellectual property or other rights that limit the facilitated access to the plant genetic resources for food and agriculture, or their genetic parts or components, in the form received from the Multilateral System;
- Access to plant genetic resources for food and agriculture under development, including material being developed by farmers, shall be at the discretion of its developer, during the period of its development; and
- Access to plant genetic resources for food and agriculture protected by intellectual and other property rights shall be consistent with relevant international agreements, and with relevant national laws.

Under Article 13 of ITPGRFA the Parties agree that benefits arising from the use, including commercial, of plant genetic resources for food and agriculture under the Multilateral System shall be shared fairly and equitably through the exchange of information, access to and transfer of technology, capacity-building, and the sharing of the benefits arising from commercialization.

The latter is achieved through a requirement in the Material Transfer Agreement that a recipient who commercializes a product that is a plant genetic resource for food and agriculture and that incorporates material accessed from the Multilateral System shall pay to a trust fund, especially established for this purpose, an equitable share of the benefits arising from the commercialization of that product. Such payment is not required when the product is available without restriction to others for further research and breeding, in which case the recipient who commercializes shall be encouraged to make such payment.

While the Multilateral System applies only to the plant genetic resources for food and agriculture set out in Annex I to ITPGRFA, genetic resources not listed in Annex I and held by the International Agricultural Centres and other international institutions, that have signed an agreement with the ITPGRFA's Governing Body, are to be exchanged under similar terms and conditions as the Multilateral System. It is to be noted that some countries now apply, on a voluntary basis, the ITPGRFA's standard material transfer agreement to plant genetic resources for food and agriculture not listed in Annex I to the ITPGRFA, which means that the conditions of the Multilateral System, ostensibly, also apply to those crops.

The Governing Body of the ITPGRFA, at its Fifth Session, decided to establish an Ad Hoc Open-ended Working Group to Enhance the Functioning of the Multilateral System of Access and Benefit-sharing with the mandate to develop a range of measures that will: (a) increase use-based payments and contributions to the Benefit-sharing Fund in a sustainable and predictable long-term manner, and (b) enhance the functioning of the Multilateral System by additional measures, which might include the possibility to expand the coverage of the Multilateral System over more crops. The Governing Body is to consider and decide on these measures at its Sixth Session in 2015.

With regard to the transfer of technology, Parties committed to providing and/or facilitating access to technologies for the conservation, characterization, evaluation and use of plant genetic resources for food and agriculture. According to the IUCN Guide to the ITPGRFA, technologies for the use of plant genetic

Source: Macroscopic Solutions, LLC

resources include both traditional plant breeding techniques and biotechnological methods, such as molecular markers and recombinant DNA technology (Moore & Tymowski 2005).

12. THE WTO AGREEMENT ON TRADE RELATED ASPECTS OF INTELLECTUAL PROPERTY RIGHTS (TRIPS)

The WTO Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) came into effect on 1 January 1995 and is to date the most comprehensive multilateral agreement on intellectual property.

12.1. Overview of main provisions

According to its Article 7 (objective), the protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations.

The TRIPS Agreement sets out the minimum standards of protection that each Member has to provide for the different areas of intellectual property, including copyright and related rights; trademarks; patents; and the protection of new varieties of plants, among others. For each area, the TRIPS Agreement defines the subject-matter to be protected, the rights to be conferred and permissible exceptions to those rights, as well as the minimum duration of protection. For components, organisms and products resulting from synthetic biology techniques, patents and protection of plant varieties are most relevant, but copyright and trademarks have also been discussed in the literature (Torrance 2010). Least developed country Members are currently not obliged to give effect to the substantive standards of TRIPS (apart from general non-discrimination principles) until 2021, a deadline that has been extended twice and may be extended again.

12.2. Patents

In general, while discovery and invention both play an important role in synthetic biology, only inventions are treated as a patentable subject matter under the TRIPS Agreement. Article 27, paragraph 1 of the TRIPS Agreement states that patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. The TRIPS agreement, however, provides no definition or interpretation of these criteria. Thus, WTO Members have considerable leeway in applying them (UNCTAD-ICTSD 2004).

The criterion of "novelty" is generally understood to mean that the invention has a new feature which must not have been disclosed or available to the public prior to the patent application date - the inventor is granted a patent for something new (UNCTAD-ICTSD 2004). In addition, the invention must not merely be something new, but also involve an "inventive step", representing a sufficient development over prior art. Depending on the standards that WTO members require for this step, this requirement can serve to exclude trivial or routine "inventions" from being patented (UNCTAD-ICTSD 2004). In this context, according to patent practice in some countries, discoveries of things already existing in nature are deemed unpatentable in their naturally occurring form, on the basis that they are mere discoveries and not inventions as such (UNCTAD-ICTSD 2004). Thirdly, the invention must be useful and capable of industrial application, which aims at a direct technical result (UNCTAD-ICTSD 2004).

It has been argued that many components, organisms and products resulting from synthetic biology techniques fulfil these criteria. In particular, while there has been some controversy in the past as to whether, for example, DNA sequences should constitute patentable subject matter, considering that they are derived from natural ("genomic") DNA sequences, novel genes constructed using synthetic biology techniques will more clearly fulfil the criteria (Torrance 2010).

While patentable inventions may in principle be found in all areas of technology, the TRIPS Agreement permits, but does not require, WTO Members to exclude on public policy grounds certain inventions from the scope of patentable subject matter, even when they otherwise meet the substantive and formal conditions for patentability. Paragraph 2 of Article 27 states that WTO members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to

Source: Macroscopic Solutions, LLC

avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law. Components, organisms and products resulting from synthetic biology techniques could therefore be excluded from patentability in the territory of a WTO member, if the prevention of their commercial exploitation in that territory is necessary in order to protect human, animal or plant life or health or to avoid serious prejudice to the environment. WTO jurisprudence has so far not addressed the specific requirements of this exception.

Some synthetic biology technologies may be considered as contrary to *ordre public* or morality in some countries. The *WTO Handbook* gives possible examples of inventions contrary to morality, such as "processes for the cloning of human beings or for modifying the germ line identity of humans." If a WTO Member considered it necessary to protect morality by preventing the commercial exploitation of components, organisms and products resulting from synthetic biotechnologies, this, too, would give grounds for their exclusion from patentable subject matter.

Article 27, paragraph 3 of the TRIPS agreement allows WTO members to exclude from patentability: (a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals; and (b) plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes. It states, however, that WTO members have to provide for the protection of plant varieties either by patents or by an effective sui generis system or by any combination thereof.

A significant focus of synthetic biology research is on medical applications – including diagnosis, therapeutic treatment, and the production of drugs and vaccines. It would appear that medical applications of synthetic biology could be excludable from patentability to the extent that they constitute diagnostic, therapeutic and surgical *methods* for the treatment of humans or animals.

"Plants and animals", which can be excluded from patentability, are understood to include plants as such (including transgenic plants), plant varieties (including hybrids), plant cells, seeds and other plant materials, as well as animals (including transgenic) and animal races (UNCTAD-ICTSD 2004). While current applications of synthetic biology are mostly in micro-organisms, synthetic biology research in mammalian and other eukaryotic cells is making rapid progress (Annaluru *et al*. 2014; Lienert *et al*. 2014; Wieland & Fussenegger 2012), and the products of such applications could fall under excludable "plants and animals". For micro-organisms which include bacteria, fungi, algae, protozoa or viruses, patents need to be available, as far as they are novel, non-obvious and useful in accordance with Article 27, paragraph 1 of the TRIPS agreement (UNCTAD-ICTSD 2004).

The possibility of excluding the patentability of "essentially biological processes" does not extend to "non-biological" processes for the production of plants or animals or any process that uses or modifies microorganisms, such as methods based on modern biotechnology like the insertion of genes in a plant (UNCTAD-ICTSD 2004). Although there is room for interpretation in the exact meaning of "essentially biological processes," the chemical synthesis of DNA sequences seems to fall outside of this.

Thus, it seems possible for select products of synthetic biology techniques to be excluded from patentability through Article 27, paragraph 3 of TRIPS.

A significant extent of the impact of intellectual property in the field of synthetic biology concerns not what formal legal standards are in place, but how intellectual property is managed – for instance, whether patents are applied for and how they are licensed. The TRIPS Agreement does not regulate this aspect directly, although it provides scope for action to deal with abusive licensing practices and provides for public policy exceptions to patent rights; hence, within the TRIPS framework, a wide spectrum of approaches to obtaining and managing patents in this area can be discerned. Accordingly, as the field of synthetic biology develops, two main models of intellectual property for synthetic biology components, organisms, products, and techniques seem to be forming (Calvert 2012). The first heavily relies on patents and is exemplified by the approach of the J. Craig Venter Institute (JCVI) (Gibson *et al*. 2008; Gibson *et al*. 2010; Glass *et al*. 2007). In the 1990s, J. Craig Venter's Institute of Genomic Research (now part of JCVI) sequenced and patented one of the smallest known bacterial genomes, *M. genitalium*. In 2007, scientists at his institute applied for a "minimal bacterial genome" patent (Calvert 2012; Glass *et al*. 2007). This patent application is still pending; NGOs and commentators have expressed concern at its attempted breadth (ETC 2007; ETC 2010; Calvert 2012).

The other main model is the BioBrickTM system, modeled on open-source software. On iGEM's Registry of Standard Biological Parts, contributing researchers post their BioBrickTM parts (DNA sequences that incorporate standardized sections) on

Source: Macroscopic Solutions, LLC

pages accessible to the general public.[110] Following a similar approach, the BioBricks Foundation has independently developed a BioBrickTM Public Agreement that is essentially a contractual agreement between "Users" and "Contributors" of parts. Contributors may hold patents on the parts, but they promise not to assert any present or future proprietary rights against users. Unlike open source software, users have no obligation to openly share the devices or parts they make with the BioBricks. They can patent novel devices if they want to, meaning that they can build private, proprietary systems on the open platform (Calvert 2012; BioBricks Foundation 2013). While modeled on open-source, this BioBrick system essentially relies on the availability of patent processes, of which researchers can decide whether or not to make use.

13. THE INTERNATIONAL CONVENTION FOR THE PROTECTION OF NEW VARIETIES OF PLANTS (UPOV CONVENTION)

The International Union for the Protection of New Varieties of Plants (UPOV) was established by the International Convention for the Protection of New Varieties of Plants (UPOV Convention). The UPOV Convention came into force in 1968 and was revised in 1972, 1978, and 1991, in order to reflect technological developments in plant breeding and experience acquired with the application of the Convention.[111] UPOV has 72 members. The main objective of UPOV is to provide and promote an effective system of plant variety protection with the aim of encouraging the development of new varieties of plants, for the benefit of society.

13.1. Overview of main provisions

The UPOV Convention sets forth standards, including national treatment, for the granting of "breeders' rights" as a sui generis form of protection for new plant varieties. A plant variety in accordance with Article 1, paragraph (vi) of the Convention is defined as a plant grouping within a single botanical taxon of the lowest known rank, which grouping, irrespective of whether the conditions for the grant of a breeder's right are fully met, can be

- defined by the expression of the characteristics resulting from a given genotype or combination of genotypes,
- distinguished from any other plant grouping by the expression of at least one of the said characteristics and
- considered as a unit with regard to its suitability for being propagated unchanged.

The Explanatory Notes on the Definition of Variety under the 1991 Act of the UPOV Convention (document UPOV/EXN/VAR/1) states as follows:

"4. The definition of "variety" under the 1991 Act of the UPOV Convention starts by stating that it is "a plant grouping within a single botanical taxon of the lowest known rank, … " thereby confirming that a variety may not, for example, consist of plants of more than one species.

"5. The definition that a variety means a "plant grouping" clarifies that the following, for example, do not correspond to the definition of a variety:

- a single plant; (however, an existing variety may be represented by a single plant or part(s) of a plant, provided that such a plant or part(s) of the plant could be used to propagate the variety)
- a trait (e.g. disease resistance, flower color)
- a chemical or other substance (e.g. oil, DNA)
- a plant breeding technology (e.g. tissue culture)."

13.2. Breeder's right

In order to be eligible for protection, a plant variety must meet the following requirements (Article 5 UPOV Convention):

- "Novelty - propagating or harvested material of the variety must not have been sold or otherwise disposed of to others, by or with the consent of the breeder in the territory of the UPOV member where the applicant seeks protection for more than one year, nor for more than four years in any other territory and six years in the case of vines and trees (Article 6).
- "Distinctness - the variety must be clearly distinguishable from any other variety whose existence is a matter of common knowledge at the time of the filing of the application (Article 7).

110 *Following an approach described as "Get & Give (& Share), see http://parts.igem.org/Help:Philosophy.*

111 *Unless otherwise stated, reference to the UPOV Convention in the following refers to the 1991 Act of the UPOV Convention.*

Source: Macroscopic Solutions, LLC

- "Uniformity - subject to the variation that may be expected from the particular features of its propagation, the variety must be sufficiently uniform in its relevant characteristics (Article 8).

"Stability - the variety is stable if its relevant characteristics remain unchanged after repeated propagation or, in the case of a particular cycle of propagation, at the end of each such cycle (Article 9 UPOV Convention). […]" Where plant varieties resulting from synthetic biology techniques fulfil these criteria, the breeder has the possibility to obtain a breeder's right, which includes that (i) production or reproduction (multiplication); (ii) conditioning for the purpose of propagation; (iii) offering for sale; (iv) selling or other marketing; (v) exporting; (vi) importing, and (vii) stocking for any of these purposes, requires the authorization of the breeder (Article 14 UPOV Convention). The breeder's right is granted by an individual UPOV member.

In addition, the breeder's right can be obtained for varieties which are essentially derived from the protected variety, a variety that requires the repeated use of the protected variety, or a variety which was not clearly distinguishable from the protected variety (Article 14, paragraph 5(a)). This may be relevant for synthetic biology as the UPOV Convention states that essentially derived varieties may be obtained for example by the selection of a natural or induced mutant, or of a somaclonal variant, the selection of a variant individual from plants of the initial variety, backcrossing, or transformation by genetic engineering (Article 14, paragraph 5 c)).

To qualify for the breeder's right, essentially derived varieties need to (i) be predominantly derived from the initial variety, or from a variety that is itself predominantly derived from the initial variety, while retaining the expression of the essential characteristics that result from the genotype or combination of genotypes of the initial variety; (ii) be clearly distinguishable from the initial variety; and (iii) except for the differences which result from the act of derivation, conform to the initial variety in essential characteristics that result from the genotype or combination of genotypes of the initial variety. Where both the essentially derived variety and the initial variety are protected by breeders' rights, the activities listed in Article 14, paragraph 1 with regard to the essentially derived variety require the authorization of both breeders (UPOV 2009a).

13.3. Exceptions to the breeder's right

Article 15 to the UPOV Convention provides for certain exceptions to the breeder's right. According to paragraph 1, compulsory exemptions address (i) acts which are both private and for non-commercial purposes; (ii) the use of a protected variety for experimental purposes; and (iii) the use of protected varieties for the purpose of breeding new plant varieties. The commercialization of a new variety would not require the authorization of the breeder of the protected variety, except where the new variety is an essentially derived variety, a variety that requires the repeated use of the protected variety or was a variety which was not clearly distinguishable from the protected variety in accordance with Article 14, paragraph 5 of the UPOV Convention. UPOV members may, under an optional exception in Article 15, paragraph 2 of the UPOV Convention, allow farmers to save harvested material for further propagation under certain circumstances (UPOV 2009b). While the TRIPS agreement leaves open the option of excluding from the scope of patentability inventions whose commercial exploitation needs to be prohibited to address these concerns, Article 17 of the UPOV Convention allows its members to restrict the free exercise of a breeder's right for reasons of public interest.

Source: Macroscopic Solutions, LLC

E. SELF-REGULATION BY THE SCIENTIFIC COMMUNITY

Self-regulation in this context does *not* mean that scientific practices are unregulated by national or other levels of government. Rather, it refers to a portion of the scientific community agreeing amongst themselves on certain conduct, generally additional to any existing legal or regulatory obligations. Self-regulation is sometimes discussed as an option *in lieu of* formal statutory oversight (see Balmer & Martin 2008), but it is rarely a matter of either/or.

In the past, scientists in biotechnology have practiced "self-regulation." In 1975, US scientists working on recombinant DNA technologies agreed to a short-lived moratorium on some aspects of their work, in the *Asilomar Declaration* (Berg *et al*. 1975). The *Asilomar Declaration* acknowledged areas of uncertainties around hazards of rDNA, and the difficulty in obtaining accurate estimates of risk. They identified broad types of experiments that could be matched with some confidence to minimal or moderate containment strategies, and chose to defer experiments on highly pathogenic organisms, toxic genes, and large scale experiments (Berg *et al*. 1975). After Asilomar, precautions for rDNA experiments gradually relaxed. Schmidt and de Lorenzo suggest this happened because few accidents occurred despite increasing use of rDNA (Schmidt and Lorenzo 2010). The Biotechnology Industry Organization explains that, as use of rDNA grew, a "culture of safety" strengthened (Erickson *et al*. 2011). The ETC Group instead sees the *Asilomar Declaration* as a strategic move to pre-empt greater government oversight and narrow the focus of concern (ETC 2007).

Synthetic biologists have talked about self-regulation but have not made any concrete agreements. The 2006 "SB2.0" international conference on synthetic biology was initially anticipated to produce an "Asilomar-like" declaration, particularly with regards to the need for screening sequences. There are differing accounts as to why the draft declaration was never voted on or passed. According to some, there was concern that a call for self-regulation would be seen as "closed-shop" governance, and that society generally is "different" now (Campos 2009; Service 2006). The ETC Group, on the other hand, claims there was internal disagreement over whether to boycott non-compliant gene synthesis companies (ETC 2007).

Some scholars argue that Asilomar-like self-governance is an inappropriate model for synthetic biology. Bennett *et al*. argue against assumptions of a cohesive community of experts that can exclude the public and make "gentleman's agreements" in today's context of aggressive patenting, internet news, and global security conditions (Bennett *et al*. 2009).

The technological approaches to commercial surveillance are voluntarily undertaken and overseen by industry. Industry bodies such as the Biotechnology Industry Organization (BIO) argue that commercial self-regulation in DNA synthesis is sufficient, because "(at) this early stage of development, synthetic biology does not pose novel threats that are fundamentally different from those faced by the current biotechnology industry" (Erickson *et al*. 2011).

Source: Macroscopic Solutions, LLC

Source: Christine Cooper

F. CONCLUSIONS

Some general principles of international law such as the duty to avoid transboundary harm, and the need to conduct an environmental impact assessment (EIA), together with the rules of State responsibility may provide some guidance relevant to addressing potential negative impacts resulting from the application of synthetic biology techniques, but would still form an incomplete basis to address all potential positive and negative impacts. There exist a range of uncertainties of their application in the absence of specific guidance.

In addition, they may not be able to address the scope of the risks associated with some forms of synthetic biology techniques. Specific potential impacts of specific synthetic biology products might violate particular rules, but this cannot be determined unless there is greater confidence in estimates of such potential impacts.

However, living organisms resulting from current synthetic biology techniques are "living modified organisms resulting from biotechnololgy" as defined by the Convention on Biological Diversity and therefore subject to its biosafety provisions (Articles 8(g) and 19). Living organisms resulting from current synthetic biology techniques also fall under the definition of "living modified organisms" under the Cartagena Protocol for Biosafety. Therefore, the requirements of the Cartagena Protocol pertaining to the transboundary movement, transit, handling and use of living modified organisms that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, also apply.

Gaps could occur where components and products resulting from synthetic biology techniques do not fall within the scope of a treaty regime. For example, components and products resulting from synthetic biology techniques that are not living modified organisms will not be subject to the requirements pertaining to the transboundary movement, transit, handling and use of all living modified organisms that may have adverse effects on the conservation and sustainable use of biological diversity contained in the Cartagena Protocol, nor the provisions on liability and redress contained in the Nagoya – Kuala Lumpur Supplementary Protocol.

A number of treaties exist which, in general, provide for mechanisms, procedures or institutions that could address potential negative effects associated with the application of synthetic biology techniques, but where no specific guidance exists for their application. For example, States may be able to establish import restrictions on components, organisms and products resulting from synthetic biology techniques in accordance with the SPS Agreement. However, while specific guidance has been developed for the application of standards to living modified organisms, for example in ISPM No. 11 under the IPPC, no such guidance exists for components and products resulting from synthetic biology techniques. In addition, treaties like the SPS Agreement focus mainly on trade-related measures, which may not be sufficient to address all potential risks associated with synthetic biology techniques.

Most regulatory mechanisms discussed in the present document were developed before the term synthetic biology became widely used and therefore they were not intended to cope with the scope and scale that some of the potential impacts of synthetic biology may have, including those with low and very low probability, but very high impacts. The only exception is the Biological Weapons Convention, which prohibits that its parties develop, produce, stockpile or otherwise acquire or retain microbial or other biological agents or toxins of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes. While some treaties include frameworks for risk assessment, sufficient information may not be available for all synthetic biology techniques to effectively conduct risk assessments. It is a matter of disagreement among synthetic biologists, ecologists, industry and civil society, how well the potential dangers related to synthetic biology are known and can be assessed.

Source: Jeffery Scism

Source: Marcus Kauffman

Synthetic biology also raises a number of questions with regard to access and benefit-sharing. This includes whether the material being accessed for use in synthetic biology can be considered "genetic resources" or "genetic material" and whether the components, organisms and products resulting from synthetic biology constitute "derivatives" as defined in the Nagoya Protocol.

The International Treaty on Plant Genetic Resources for Food and Agriculture may also be relevant to synthetic biology with regard to the access to genetic resources for use in synthetic biology processes and the sharing of the benefits arising from commercialization. Its Article 12 requires parties to provide facilitated access to plant genetic resources for food and agriculture to other parties, including to legal and natural persons under their jurisdiction. This access is to be granted pursuant to a standard material transfer agreement (MTA) through the Multilateral System under certain conditions. Synthetic biology research that does not include chemical, pharmaceutical and/or other non-food/feed industrial uses can access, in accordance with the relevant provisions of the ITPGRFA, the plant genetic resources for food and agriculture listed in Annex I to the Treaty, a pool of 64 food and forage crops. These plant genetic resources and their genetic parts and components cannot be protected through an intellectual property right that limits the facilitated access to them, in the form received from the Multilateral System.

It appears that, in accordance with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), patents should be available under national law of WTO members (other than LDCs) for innovative products and techniques in the field of synthetic biology, provided that they constitute inventions that comply with the general patentability standards. The results of current synthetic biology research that is focused on modifying existing "natural" genomes could also qualify for the "breeder's right" (a sui generis form of protection for intellectual property rights on plant varieties) under the UPOV Convention. As far as synthetic biology research may in the future result in the production of entirely novel genomes, it may be able to produce new plant varieties which could be protected by breeder's rights, including varieties that are deemed essentially derived from a protected variety.

In sum, the components, organisms and products resulting from synthetic biology would fall under the scope of a number of regulatory mechanisms. While some instruments are sufficiently broad to address some of the current issues related to synthetic biology, gaps still exist relating to the practical implementation of these instruments to ensure the conservation and sustainable use of biodiversity, and the fair and equitable sharing of the benefits arising from the utilization of genetic resources. Discussions in international fora may be needed with a view to addressing the gaps identified in this document in an appropriate, consistent, comprehensive and adaptive manner. This could include a need to consider how to address potential impacts of very low probability but very high magnitude. Further discussions may also be needed if and when the advances in synthetic biology lead to the emergence of new gaps.

Source: Jeffery Scism

Source: BASF

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