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CONFERENCE OF THE PARTIES TO THE
CONVENTION ON BIOLOGICAL DIVERSITY
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Item 24 of the provisional agenda*

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

Note by the Executive Secretary

BACKGROUND

1. In decision XI/11 on new and emerging issues relating to the conservation and sustainable use of biodiversity the Conference of the Parties took note of the proposals for new and emerging issues relating to the conservation and sustainable use of biodiversity and requested the Executive Secretary to:

(a) Invite Parties, other Governments, relevant international organizations, indigenous and local communities and other stakeholders to submit, in accordance with paragraphs 11 and 12 of decision IX/29, additional relevant information on components, organisms and products resulting from synthetic biology techniques that may have impacts on the conservation and sustainable use of biological diversity and associated social, economic and cultural considerations;

(b) Compile and synthesize relevant available information, together with the accompanying information;

(c) 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;

(d) Make a synthesis of the above information, including an analysis of how the criteria set out in paragraph 12 of decision IX/29 apply to this issue, available for peer review and subsequent consideration by a meeting of the Subsidiary Body on Scientific, Technical and Technological Advice prior to the twelfth meeting of the Conference of the Parties, in accordance with paragraph 13 of decision IX/29;

2. In response this decision the Executive Secretary issued notification 2013-0181 inviting additional information on synthetic biology and undertook a review of information in accordance with paragraph 5 of decision XI/12 with a view to enabling the Subsidiary Body on Scientific, Technical and Technological Advice to consider the proposal.

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* UNEP/CBD/COP/12/1/Rev.1.

1 Available at http://www.cbd.int/doc/notifications/2013/ntf-2013-018-emerging-issues-en.pdf.

3. An earlier version of this note was made available for the information of the eighteenth meeting of the Subsidiary Body on Scientific, Technical and Technological Advice as UNEP/CBD/SBSTTA/18/INF/3. The information note was developed taking into account peer review comments received from July to September 2013, and in April 2014.

4. The current note is a substantially revised version that takes into account comments made at the eighteenth meeting of the Subsidiary Body on Scientific, Technical and Technological Advice and additional peer review comments received in July and August 2014.

5. It is accompanied by a second document focusing on gaps and overlaps with the applicable provisions of the Convention and its Protocols (made available as UNEP/CBD/COP/12/INF/12)2 for the information of the twelfth meeting of the Conference of the Parties to the Convention on Biological Diversity.

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

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A. EXECUTIVE SUMMARY

1. **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.

2. **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:

(a) **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;

(b) **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;

(c) **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;

(d) **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);

(e) **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.

3. **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.

4. **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:

(a) The development of micro-organisms designed for bioremediation and biosensors resulting in pollution control and remediation of environmental media;

(b) 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;

(c) Developing organisms designed to generate biofuels which may lead to decreased dependence on non-renewable energy sources;

(d) 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;

(e) Restoring genetic diversity through reintroducing extinct alleles, or even “de-extinction” of species.

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

(a) 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;

(b) 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”);

(c) Possible toxic and other negative effects on non-target organisms such as soil micro-organisms, beneficial insects, other animals and plants;

(d) 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.

6. **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.

7. **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 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.

8. **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.

9. **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.

10. **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.

11. **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.

12. **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.

13. **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.

B. PREAMBLE

14. 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.

15. During the peer-review process of this document, many reviewers noted that current and near-term[3] 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".

16. 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.

C. TECHNICAL BACKGROUND ON SYNTHETIC BIOLOGY

1. Introduction

17. 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.

18. 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.4 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).

19. 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).

20. 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

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

[4] 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.

Massachusetts Institute of Technology (MIT, USA) hosted "the First International Meeting on Synthetic Biology," SB1.0.[5] In 2007 the number of annual academic publications on synthetic biology first *exceed*ed 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.[6] 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 Framework programme, and the Human Frontier Science Foundation.[7] 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).

21. 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.8 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).

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

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

7 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).

8 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.

Box 1. Definitions 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)

SB 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

22. 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).

23. 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).

24. 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 examples, 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).[9] 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).

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[9] See http://wyss.harvard.edu/viewpage/330/, accessed on 23 March 2013.

25. 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 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

26. 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).

27. The areas of research that are considered "synthetic biology" 10 include DNA-based circuits, synthetic metabolic pathway engineering, synthetic genomics, protocell construction, and xenobiology.

3.1. DNA-based circuits

28. 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).

29. 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

[10] Other areas of research sometimes included within SB 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 SB is discussed, and commentators have not addressed them in terms of their implications for ethics, biosafety, biosecurity, or other aspects.

systems. A major platform for demonstrated uses of BioBricks™ has been the annual International Genetically Engineered Machine competition (iGEM).[11] The iGEM Foundation (which runs the competition) also hosts an open website, the Registry of Standard Biological Parts,[12] 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.[13] 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 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".[14]

30. 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).15 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).16 In 2013, BIOFAB announced that its researchers had established mathematical models to predict and characterize "thousands of high quality standard biological parts".17

3.2. Synthetic metabolic pathway engineering

31. 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

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

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

13 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.

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

15 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).

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

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

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.

32. 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 bellow 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-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

33. This area of synthetic biology research focuses on the genome as the "causal engine" of the cell (O'Malley *et al.* 2007).[18] 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.

34. 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).

35. 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

[18] 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 SB.

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

36. 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).

37. 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

38. 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).[19] 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).

[19] Joyce (2012) also describes this as "alternative biology."

39. 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, 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.

40. 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

41. 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

42. 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).

43. 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.[20] 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.[21] Registered iGEM teams and laboratory groups can order samples of other parts not included in the Distribution Kit by writing to the iGEM Foundation.[22]

4.2. Products from synthetic biology

44. 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).

4.2.1. Production of molecules that are otherwise produced from petroleum

45. 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.

46. 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.[23] 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.[24] 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.[25]

47. 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

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

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

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

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

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

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

Lyle BioProducts have been producing Bio-PDO™ (1,3-propanediol) since 2006, using corn as feedstock and proprietary microorganisms.[26] 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*.[27] 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).[28]

48. 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

49. 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).

50. "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[29] and Isobionics[30] 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).[31]

51. 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[32] 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).

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

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

28 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).

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

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

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

32 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.

52. 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).

53. 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".

54. 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

55. 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).

56. 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

57. 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.

58. New companies are starting to offer "made to order" microorganisms, produced in part using synthetic biology. For example, Ginkgo BioWorks™ 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™[33] 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 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

[33] See: http://ginkgobioworks.com/tech.html, accessed 6 March 2013.

National Institute of Standards and Technology), and ARPA-e (the US Advanced Research Projects Agency – Energy).[34]

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

59. 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.

60. 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.[35] 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).

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

61. 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.

62. 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

63. 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.

64. 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

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[34] See: http://ginkgobioworks.com/partner.html, accessed 23 March 2013.

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

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 (page). Biosafety concerns of a more general nature are examined in section 6.

5.1. **Bioenergy applications**

65. 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).

66. 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.[36] 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).

67. 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

[36] See: http://www.cbd.int/climate, accessed 13 Feb. 2014.

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).

68. 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 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

69. Another area of synthetic biology research is in environmental applications, most of which would require environmental release or contained use[37] 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.[38]

70. 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

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[37] "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.

[38] 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 SB are discussed. Dana *et al.* (2012) cite this project in their article on designing appropriate biosafety systems for SB.

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.

71. 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).

5.3. Applications to alter wildlife populations

72. 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.[39] 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.[40] 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,

[39] 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.

[40] 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/.

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).

73. 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.[41] 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).

74. 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 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).

75. 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.[42] 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

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

[42] 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).

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

76. 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 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.[43]

77. 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).

[43] 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).

5.5. Applications to replace natural materials

78. 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).[44]

79. 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.[45] Companies point to the price volatility and limited availability of the squalene sourced from olives, and some manufacturers continue to use deep sea sharks, 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.[46] 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.

80. 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,[47] and hope to have a competitive advantage over other synthetic forms of vanillin, which are currently produced from 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

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[44] Many national biosafety frameworks regulate these micro-organisms under provisions for GMOs/LMOs destined for contained use.

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

[46] 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.

[47] 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.

plantations to monoculture sugar plantations (for feedstock for synthetic biology processes) is an improvement for biodiversity (ETC 2013a).

5.6. Applications for chemical production

81. 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.[48] 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).

82. 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

83. 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

84. 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 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

[48] 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 SB techniques. Esvelt & Wang identify DuPont's work on propanediol as a "great example of genome-level metabolic engineering" (2013).

for biofuel production escaped containment and bloomed (Redford *et al.* 2013; Snow and Smith 2012; Wright *et al.* 2013).

85. 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).

86. 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

87. 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).

88. 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.

89. 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.

90. 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

91. 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".

92. 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

93. 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

94. 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.

95. 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.

96. 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).[49] 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".[50]

97. 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.[51]

7.2. Biological containment

98. 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.

99. 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

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[50] Available at http://www.geneticsandsociety.org/article.php?id=5517.

[51] 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.

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".

100. 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 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).

101. 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).

102. 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, let alone 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).

103. 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.

104. 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

105. 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.

106. 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 their careers in laboratories. For example, the annual iGEM competitions involve college and high school students in synthetic biology experiments (Guan *et al.* 2013).[52]

107. 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).

108. 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).

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

8. Adequacy of current methodologies for environmental risk assessment

109. 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,[53] they are inadequate for organisms produced using synthetic biology techniques that have no analog in the natural world.

110. 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.

111. 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

[53] 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."

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.

112. 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).

113. 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.

114. 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.[54]

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

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

Specific area of application	Potential positive and negative impacts* on conservation and sustainable use of biodiversity
	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
Wildlife-targeted applications of synthetic biology	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 (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") 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)

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.

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

115. 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

116. 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.

117. 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).[55] 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).

118. 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.

119. 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).[56] Mukunda *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.

120. 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

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

[56] 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 SB. 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.

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

121. 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%.[57] 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).

122. 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).[58] Civil society groups' definitions of the bioeconomy are similar to that of the European Commission.[59] 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).

123. 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-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).

124. 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

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

[58] 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).

[59] 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).

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.[60] 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.[61]

125. 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).

126. 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.

127. 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 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

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[60] 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.

[61] See http://www.mysinchew.com/node/81046. Accessed on 23 April 2013.

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.[62]

128. 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).[63] 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).

129. 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[64] 2014 personal commun.). 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.[65] 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.

130. 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

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

63 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.

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

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

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 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).

131. 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).

132. 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

133. 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.

134. 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.

135. 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.

136. 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

137. 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)).

138. 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.

139. 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.

140. 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).

141. 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).

142. 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.

143. 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

144. 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).

145. 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).

146. 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

Social, economic and cultural considerations	Possible positive and negative impacts of synthetic biology
	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)
	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 possiblity 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*

Social, economic and cultural considerations	Possible positive and negative impacts of synthetic biology
	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)

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