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NEW AND EMERGING ISSUES RELATING TO THE CONSERVATION AND SUSTAINABLE USE OF BIODIVERSITY - POTENTIAL POSITIVE AND NEGATIVE IMPACTS OF COMPONENTS, ORGANISMS AND PRODUCTS RESULTING FROM SYNTHETIC BIOLOGY TECHNIQUES ON THE CONSERVATION AND SUSTAINABLE USE OF BIODIVERSITY

INTRODUCTION

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 2013-018 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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3. This note is based on an earlier draft, which has been revised and completed in the light of comments and suggestion received through a peer review process. Peer-review comments had been received from five Parties, one other Government and from six organizations.[1]

4. It is accompanied by a second document focusing on gaps and overlaps with the applicable provisions of the Convention and its Protocols (UNEP/CBD/SBSTTA/18/INF/4).

[1] Peer-review comments are accessible from http://www.cbd.int/emerging/

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EXECUTIVE SUMMARY

1. **One of the most commonly cited definitions of synthetic biology is "the design and construction of new biological parts, devices, and systems" and "the re-design of existing, natural biological systems for useful purposes."** Although there is no legally accepted definition, there is general agreement that synthetic biology aims: to *exercise control* in the design, characterization and construction of biological parts, devices and systems, leading to *more predictable* designed biological systems. Key features of synthetic biology include chemical synthesis of genetic sequences and an engineering-based approach. Synthetic biology represents a shift in the driving forces of biology, from discovery and observation to hypothesis and synthesis. Sometimes described as a "converging technology," synthetic biology brings together and builds on the fields of engineering, molecular biology, systems biology, nanobiotechnology, and information technology.

2. **Products of synthetic biology are often made using multiple techniques of synthetic biology and "conventional" biotechnology more broadly. Currently, the majority of current and near-term commercial and industrial applications of synthetic biology use synthetic DNA-circuits and synthetic metabolic pathway engineering to create microbes that produce molecules for pharmaceuticals, fuels, chemicals, flavorings and fragrances.** The following areas of research are commonly considered "synthetic biology": DNA-based circuits, synthetic metabolic pathway engineering, genome-level engineering, protocell construction, and xenobiology. Some see the insertion of synthetically designed and produced DNA sequences or pathways into an existing genome largely as rebranding conventional biotechnology. Others consider the building of non-natural pathways that would be difficult to achieve with traditional genetic engineering and the *systematic* engineering circuits and pathways as approaches novel to synthetic biology and distinct from traditional genetic engineering.

3. **Synthetic biology could provide more efficient and effective tools to respond to modern challenges, such as responding to biosecurity threats and diagnosing and treating diseases. Current, near-term and anticipated applications of synthetic biology in areas such as bioenergy, environment, wildlife, agriculture, chemical production, biosecurity, and health will have direct impacts specific to each application.** Some of these applications are anticipated to specifically target the conservation and use of biodiversity, either with intended positive impacts (for example, greener industrial processes, de-extinction, bioenergy) or with intended negative impacts (for example, bioterror). Unintentional but direct harm might be experienced, for example if medicines and therapies resulting from synthetic biology techniques trigger unanticipated adverse effects on human health or if synthetic biology laboratory workers are accidentally exposed to components or organisms.

4. **Current and near-term applications of synthetic biology are mostly intended for contained use in research labs and industrial settings. Under these circumstances they are mostly not seen as raising biosafety concerns different from conventional genetic engineering.** Biosafety concerns regarding unintentional releases of these organisms, such as yeast engineered to produce the active ingredient of a natural antimalarial or a bacteria engineered to produce an industrial solvent, are largely not seen as different from those related to conventionally genetically-modified organisms. Some ecologists note that, as micro-organisms have a high potential for evolutionary change, even ones that are unlikely to survive outside of contained use may evolve to become more successful in the environment, and thus represent a potential biosafety concern. Also, some multicellular organisms resulting from synthetic biology techniques intended for environmental release are in near-term production and anticipated for a variety of uses, including crops engineered for efficient conversion into biofuel and insects designed to control pest populations.

5. **Potential future applications of synthetic biology that could provide benefits for the conservation and sustainable use of biodiversity – micro-organisms designed for bioremediation, to enhance agricultural efficiency, to halt desertification, to cure wildlife diseases, etc. – would require the environmental release of micro-organisms resulting from synthetic biology techniques. These products involve the deliberate environmental release of organisms modified for specific purposes, and therefore raise different biosafety concerns than those of organisms engineered for contained**

uses. Since the 1980s, genetically engineered strains of micro-organisms have failed to survive in indigenous microbial communities. If synthetic biology succeeds in producing sufficiently hardy micro-organisms, they could present new biosafety concerns through their potential to transfer synthetic DNA, adapt and evolve to new environments, and impact other organisms in the ecosystem. The ability to address these concerns is constrained by our comparatively limited understanding of these processes in micro-organisms as opposed to multicellular organisms.

6. **If applications of synthetic biology significantly expand in production, this could lead to significant environmental impacts, both intended and unintended.** For example, biofuel production, a significant focus of synthetic biology research, could lead to a shift in global reliance from fossil fuels to biomass, with the intention of cutting harmful greenhouse gas emissions. Such a significant additional demand on global biomass sources, however, may lead to unsustainable extraction from agricultural lands and natural ecosystems and displace traditional users of biomass. After considering the impacts of indirect land use change and other factors the net effect on greenhouse could be positive or negative. Particularly considering that many proposed applications of synthetic biology would involve deliberate environmental release, some commentators have noted the need for biologists and others familiar with the complexities of ecosystems to engage with synthetic biology projects.

7. **Considering the current status of commercialization and application, existing regulatory regimes and risk assessment methodologies for genetically modified organisms and living modified organisms may be sufficient in most cases of current products and organisms of synthetic biology. As synthetic biology develops, this assessment will need to be revisited.** Some techniques, such as the use of a gene gun to insert synthetic DNA, do not trigger a regulatory response in some jurisdictions. Some believe that synthetic biology techniques are already advanced enough to necessitate such a reassessment. Synthetic biology techniques can be used to insert hundreds or thousands of traits from different donor organisms, which then interact with each other, challenging assessments based on assessing the risks of comparable counterparts of donor and parent organisms, although currently commercialized organisms largely do not utilize such a full range of complexity. Some researchers reflect a 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.

8. **There is debate over the degree and probability of harm that organisms resulting from synthetic biology techniques intended for contained use could cause if released.** There is a low probability that synthetic biology organisms which were engineered for contained use and which are released accidentally could survive and propagate. On the other hand, the majority of research in synthetic biology uses microbes as hosts which have a particularly high potential for mutations. Once released into the environment these organisms cannot be retrieved and could potentially represent a catastrophic risk. Such a low-probability and high-consequence situation raises ethical issues around harms, benefits and risks.

9. **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."** Some of these strategies to engineer biosafety rely on xenobiology, the replacement of the genetic alphabet of DNA with novel informational biopolymers or with unnatural base pairs which are not expected to be able to interact with natural forms of life on the genetic level. Although promising, the science of xenobiology is not yet able to demonstrate containment, and significant research challenges remain.

10. **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 manufacturing and economic paradigm shifts.** Synthetic biology could be a key technology in developing economies in which biotechnology contributes a significant share or economies using

biological resources and bio-based processes. How developing countries would fare in such a global "bioeconomy" is not self-evident. Synthetic biology could benefit the health and economies of developing countries through specific applications, and 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 could reinforce inequitable trends in international trade, that the scale of extraction and use of biomass for a global bioeconomy could be ecologically unsustainable and threaten traditional economies reliant on biomass, and that natural products currently grown or harvested will be displaced by industrial production from micro-organisms resulting from synthetic biology techniques. The shape of new bioeconomies and the fates of their ecological and human communities can be influenced by government regulations and economic instruments.

11. **Ethical issues are invoked by specific applications of synthetic biology and, more generally, synthetic biology techniques.** Specific applications of synthetic biology such as "de-extinction" projects 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 *in situ* conservation might be seen as less pressing due to the expectation that 'lost' species can be resurrected. More broadly, the increased capabilities of synthetic biology techniques raise ethical issues. Ethicists debate whether we have already crossed the threshold from the modification of existing organisms to the creation of *de novo* organisms, and what the ethical implications of this might be. How should such new organisms be valued? Does synthetic biology move humanity towards instrumentalism, where organisms are assigned value based on their instrumental use? Could this influence the ethical basis for conservation, or influence public perceptions of what is "natural"? Like other biotechnologies, synthetic biology raises ethical questions around the level of predictability of its positive and negative impacts that should be required, and how to weigh anticipated impacts and the possibility of unexpected impacts.

12. **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 components, organisms, products, and techniques seem to be forming: heavy reliance on patents and a system modeled on open-source software that enables a combination of patenting and shared use of designed DNA sequences. Depending on the intellectual property rights regimes, innovation in synthetic biology may be encouraged, stifled, or directed towards certain kinds of applications or users.

I. TECHNICAL BACKGROUND ON SYNTHETIC BIOLOGY

1.1 Overview and definitions for synthetic biology

13. **One of the most commonly cited definitions of synthetic biology is: (i) the design and construction of new biological parts, devices, and systems, and (ii) the re-design of existing, natural biological systems for useful purposes.**[2] Key features of synthetic biology include chemical synthesis of genetic sequences and an engineering-based approach. It is important to note that there is no legally accepted definition of synthetic biology, and the existence of a singular definition is debated in academia (see Box 1: Definitions of Synthetic Biology). There is, however, general agreement on its goals: to exercise control in the design, characterization and construction of biological parts, devices and systems, leading to more predictable designed 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, systems biology, nanobiotechnology, and information technology (EGE 2009; PCSBI 2010; RAE 2009).

14. **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, 1). Weber and Fussenegger refer to it as "analysis by synthesis" (2012, 22). 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).

15. **Synthetic biology is a young field that has experienced rapid growth in the past decade with government and industry support.** The current use of the term "synthetic biology" arose in the early 2000s to distinguish the emerging area of science from conventional genetic engineering (O'Malley *et al.* 2007; Campos 2009). In 2004, the Massachusetts Institute of Technology (MIT, USA) hosted "the First International Meeting on Synthetic Biology," SB1.0.[3] In 2007 the number of annual academic publications on synthetic biology first exceeded 100 (Oldham *et al.* 2012). The global synthetic biology market was estimated by forecasters to be $1.1 billion in 2010, and predicted to be $10.8 billion by 2016.[4] Forty countries are in the "core landscape of research" on synthetic biology; most research happens in the USA and European countries, but other sites of major research include China, Brazil, India, Mexico, Argentina, South Africa and Singapore (Oldham *et al.* 2012, 5). 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.[5] A 2013 mapping of synthetic biology research and commercial production by the Woodrow Wilson International Center for Scholars (WWICS 2013a) found a total of 508 unique entities conducting synthetic biology research, with 192 companies and 204 universities. The top five application focuses of designers/manufacturers conducting synthetic biology research were:

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

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

[4] See *Synthetic Biology: Emerging Global Markets*, at http://www.bccresearch.com/report/global-synthetic-biology-markets-bio066b.html. Accessed on 17 April 2013. An indication of the money related to SB is the cost of BCC Research's report: $5450 for a single user license, up to $9350 for an enterprise license. Another recent market report estimated the 2012 SB market value at 2.12 billion USD. See: http://www.transparencymarketresearch.com/synthetic-biology-market.html, accessed on 24 Feb. 2014.

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

medicine; specialty/fine chemicals; fuels and fuel additives; plastics, polymers and rubbers; and plant feedstocks for microbe consumption (WWICS 2013a).

16. **Disagreement over a definition for synthetic biology is tied to differing views of the novelty of the field of synthetic biology and its relationship with "conventional" biotechnology** (Nielsen & Keasling 2011; PCSBI 2010; Zhang *et al.* 2012). The relationship between synthetic biology and previous biotechnology tends to be described differently based on the audience. When talking to regulators and the public, synthetic biologists tend to emphasize "continuity with the past" and safety; when talking to prospective funders, they emphasize novelty (Tait 2009, 150). Even within scientific communities, there are differences of opinion 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. Currently, the majority of current and near-term commercial and industrial applications of synthetic biology use synthetic DNA-circuits and metabolic pathway engineering to create microbes that produce molecules for pharmaceuticals, fuels, chemicals, flavorings and fragrances (Wellhausen and Mukunda 2009). These two approaches are rooted in "conventional" biotechnology; depending on one's perspective, many of those applications could be considered "conventional" and not synthetic biology. From that perspective, synthetic biology is almost entirely restricted to research labs.[6] From a broader view, commercial, industrial, and research applications of synthetic biology are already happening and are rapidly proliferating (Industrial Biotechnology 2014). Expectations for the future of synthetic biology also differ. If synthetic biology lives up to its potential, predictable and rational design of biological components and systems could usher in a new paradigm for biology (Zhang *et al.* 2011). But it's unclear whether or how soon this will happen. Scientific understanding of most genes is still quite limited; the ability to forward engineer is currently limited to a handful of genes (Schmidt & de Lorenzo 2012; Weber & Fussenegger 2012). Many of the future synthetic biology applications that represent potential positive impacts for biodiversity would require environmental release, and thus pose different challenges to biosafety than current uses (Anderson *et al.* 2012).

[6] For example, Party reported in its 2013 submission 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, 2029)

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, 36)

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, 8)

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, 25)

European Group on Ethics in Science and New Technologies to the European Commission.

1. the design of minimal cells/organisms (including minimal genomes);

2. the identification and use of biological ‘parts’ (toolkit);

3. the construction of totally or partially artificial biological systems.

In addition, several experts emphasize the potential of synthetic genomics. Synthetic genomics may be defined as a field within synthetic biology that uses the increasing wealth of genomic information including the tools of oligonucleotide synthesis and of genetic modification with the aim of producing new genomes that will allow the fabrication of a product or a desired behaviour. (EGE 2009, 14).

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, 13).

1.2 Supporting technologies

17. **Synthetic biology relies on a suite of supporting technologies 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 possible simulation 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 analyze DNA since the 1970s, but high-throughput and “next generation” sequencing methods make it possible to read longer lengths of DNA at much faster speeds for less money. 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 other levels (Pauwels *et al.* 2012).

18. The ability to chemically ***synthesize DNA*** also dates from 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 constructed DNA for experiments (Garfinkel and Friedman 2010; Schmidt 2009). Oligonucleotides, short strands from 25 to 100 base pairs of nucleotides, can still be produced in individual labs, but it is becoming far more common for labs to simply order DNA from commercial companies (Garfinkel *et al.* 2007). Using proprietary techniques, machines can create DNA strands up to the size of a gene, thousands of base pairs in length. Techniques for ***DNA assembly*** have also advanced, with labs 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 sequences in a single reaction (Gibson *et al.* 2009). DNA fabrication 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; Schmidt 2010). J. Craig Venter has described the movement of biological information onto and out of computers "biological teleportation": sequencing on-site genomes, sending sequences into the cloud, and converting them back into DNA sequences (Industrial Biotechnology 2014).

19. ***Directed evolution*** is a biotechnology method often employed for synthetic biology (Cobb *et al.* 2012; Erickson *et al.* 2011). Researchers apply selective pressure to a range of variations of a biological entity, with the goal of identifying those with desired properties. This can be done physically in the lab or on a computer (*in silico*), using bioinformatic tools to predict the fitness of sequences (Cobb *et al.* 2012). In "gene knockout," single or multiple genes are removed from a genome (Burgard *et al.* 2003). Another technique is "gene shuffling," in which DNA is randomly fragmented and reassembled, and the results tested for such properties as increased enzyme activity and improved properties of specific proteins. (Skerker *et al.* 2009). "Genome shuffling" rapidly evolves whole microbes. For example, Harvard's Wyss Institute has developed a technology called multiplex automated genome engineering (MAGE).[7] They used MAGE to optimize a pathway in *Escherichia coli*, simultaneously modifying 24 genetic components, producing over 4.3 billion combinatorial genomic variants per day, which were then screened for desirable traits (Wang *et al.* 2009). Such techniques can be applied to microbes already transformed with or built from synthetic DNA, as a way to further fine tune for specific results, and can also be used for de novo protein synthesis (Pauwels *et al.* 2012). Synthetic biology employs these and other novel approaches to genetic manipulation, such as targetable nucleases (zinc finger nucleases, transcription activator-like effector nucleases (TALEN), and clustered regularly interspaced short palindromic repeats (CRISPR) that are RNA-guided) that can be engineered to bind to specific DNA sequences (Carroll 2013; Lienert 2014).

1.3 Areas of synthetic biology research

20. **Although they are not consistently categorized, the following areas of research are commonly considered "synthetic biology"[8]: DNA-based circuits, synthetic metabolic pathway engineering, genome-level engineering, protocell construction, and xenobiology.** Although "synthetic biology" is often spoken of as a coherent, single discipline presenting uniform benefits and dangers, these different types of synthetic biology represent different potential impacts, both negative and positive, on biodiversity-related issues.

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

[8] 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.

1.3.1 DNA-based circuits

21. **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**,** 280). 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 are sometimes considered to be in the same category because DNA-based circuits are often deployed in engineering metabolic pathway changes (Pauwels *et al.* 2012).

22. **This is the area of synthetic biology that most directly aims to "make biology into an engineering discipline"** (O'Malley *et al.* 2007, 57). Bioengineer Drew Endy's foundational 2005 paper in *Nature* applied three ideas from engineering to biology: *standardization* of basic biological parts and conditions to support their use; the *decoupling* of design from fabrication; and using hierarchies of *abstraction* so that one could work at a specific level of complexity without regard to other levels. One of the earliest and highest profile standardization systems for the design of DNA "parts" was established by scientists and engineers at MIT in 2003. "BioBricks™," sequences of DNA encoding a biological function, are intended to be modular parts that can be mixed and matched by researchers designing their own devices and systems. MIT hosts an open website, the Registry of Standard Biological Parts[9], where researchers share code for parts designed following BioBrick™ standards. A major platform for demonstrated uses of BioBricks™ has been the annual International Genetically Engineered Machine competition (iGEM).[10] Since 2004, iGEM has provided a platform for undergraduate students to build biological systems using existing BioBricks™ and designing original parts.[11] It has grown rapidly, launching a high school division in 2011 and an Entrepreneurial Division in 2012. The 2012 iGEM competition had 190 teams, with over 3000 participants from 34 countries. Thanks to the Open Registry 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 (O'Malley *et al.* 2007; Collins 2012; ECNH 2010; PCSBI 2010). Although the Open Registry is non-profit, there are also commercial companies using proprietary systems to produce libraries of modular parts. For example, Intrexon, a privately held biotechnology company, advertises its "UltraVector® platform" which uses "a dynamic library of more than two million diverse, modular genetic components (to) enable the discovery, design, assembly and testing of a wide spectrum of multigenic biological systems" (Intrexon Corp. 2013b).

23. **The current reality of DNA circuit construction is far from the simplified modularity of engineering; but modularity continues to be promised on the near-horizon.** In 2006, Heinemann & Panke noted that the design process for genetic networks was still an iterative process, containing "considerable elements of trial and error" (2006, 2795). In 2012, this was still the case, as Schmidt & de Lorenzo 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

[9] For years this was hosted at http://partsregistry.org. As of 27 May 2013, the Registry is hosted at http://parts.igem.org, on the iGEM site. Accessed 04 June 2013.

[10] See http://igem.org/About, accessed 22 Feb. 2013.

[11] As discussed in section 2.2.2.3 on social aspects of containment, the iGEM competition also requires that participants reflect upon potential impacts of their projects.

Registry of Standard Biological Parts includes thousands of parts, but many are undefined, incompletely characterized, and/or don't work as described (Kwok 2010; Baker 2011). 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.[12] In 2009, BIOFAB: International Open Facility Advancing Biotechnology (BIOFAB) was formed 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 and b).13 In 2013, BIOFAB announced that its researchers had established mathematical models to predict and characterize parts (Mutalik *et al.* 2013 a and b).

1.3.2 Synthetic metabolic pathway engineering

24. **This area of synthetic biology research aims to redesign or rebuild metabolic pathways, to synthesize a specific molecule from a "cell factory"** (Lam *et al.* 2009; Nielsen and Keasling 2011). There is disagreement over whether this is synthetic biology or a conventional biotechnology practice (metabolic engineering) rebranded as such to take advantage of the hype over synthetic biology (Porcar and Pereto 2012; Various 2009, 1071). Nielsen and Keasling (2011) explain that, in conventional metabolic engineering, an organism that naturally produces the desired chemical is improved through strain breeding or genetic modification to increase production. Synthetic biology enables scientists to start with a "platform cell factory" that would not naturally produce *any* of the chemical. A synthetic pathway (rationally designed or based on a natural sequence but computer 'optimized') is added to the cell, and then conventional metabolic engineering tools may be used to increase the desired output (Nielsen and Keasling 2011; Venter 2010). Some claim that the aim to *systematically* engineer metabolic interactions sets it apart from conventional metabolic engineering (Arkin & Fletcher 2006; Lam *et al.* 2009). It can also be seen as different in that synthetic biology tools make it possible to build non-natural pathways that would be difficult to produce with traditional genetic engineering techniques (Pauwels *et al.* 2013).

25. **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 1.4 fall 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 baker's yeast (*Saccharomyces cerevisiae*), to produce substances such as fuels (such as Amyris' Biofene), medicines (such as Sanofi's semi-synthetic artemisinin), and fragrances (such as Evolva's vanillin). Hosts beyond bacteria and yeast are also being explored; for example, the proteins for production of spider silk have been expressed in plants such as *Arabidopsis* (Yang *et al.* 2005) and in the milk of transgenic animals such as mice with a synthetic gene encoding for dragline silk protein (Xu *et al.* 2007).[14]

1.3.3 Genome-level engineering

26. **This area of synthetic biology research focuses on the genome as the "causal engine" of the cell** (O'Malley *et al.* 2007).[15] Rather than designing short DNA sequences or engineering for specific

[12] See http://2013.igem.org/Welcome, accessed on 16 Jan. 2014.

[13] See http://www.biofab.org, accessed on 25 March 2013.

[14] Neither of these studies explicitly describe their work as "synthetic biology," but have been cited as examples of SB by others. Yang *et al.*(2005) is cited as an example of SB in de Vriend (2006) and Xu *et al.* (2007) is cited as an example of SB in Lam *et al.* (2009).

[15] 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.

metabolic pathways, researchers work at the whole-genome level. There are two strategies to genome-level engineering: top down and bottom up.

27. **Top-down genome-engineering 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 (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 remain with functions that are simply not understood (Lam *et al.* 2009). Porcar and Pereto argue that we are "still far" from a true chassis (2012, 81).

28. **Bottom-up genome-engineering aims to build functional genomes from pieces 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 published the successful synthesis and assembly of a 1.08 million base pair bacterial genome of *Mycoplasma mycoides*, 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 traditional genome engineering, because they had produced cells "based on computer-designed genome sequences" (*Ibid*., 55). Others have pointed out that the synthetic genome was almost entirely copied from an existing genome; *de novo* organisms are not being designed (Porcar and Pereto 2012). Natural genomes are needed as models because many DNA sequences are necessary but have unknown functions. As Gibson *et al.* (2010) acknowledge, there is still no single cellular system in which the biological roles of all of the genes are understood. Still, the authors argue that their success paves the way for synthesizing and transplanting more novel genomes (Gibson *et al.* 2010). And, by assembling the longest genome yet from synthetic DNA, the JCVI researchers' *in vivo* (in cell) assembly demonstrated a way to bypass the length-limits of DNA synthesis machines (Ma *et al.* 2012). Scientists with the "Sc2.0" project are aiming to synthesize a eukaryotic genome, the yeast *S. cerevisiae*.[16] In 2011, Dymond *et al.* published successful work in replacing sections of two chromosomes of *S. cerevisiae* with synthetic DNA.

1.3.4 Protocell construction

29. **Like the search for a minimal genome, researchers seeking to create a protocell are driven to design for less complexity, although at the *cellular* level rather than the genome.** 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, 145). 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 do away with the cell altogether to provide a more controllable biochemical context for synthetic biology devices (RAE 2009; Pauwels *et al.* 2013).

30. **Research in this area is vibrant, but thus far restricted to basic research.** Although many protocell scientists are seeking to identify new biotechnology production systems, much protocell research is intended to explore the origin of life (Budin & Szostak 2010; Lim *et al.* 2012; Schmidt 2010). Potential protocell applications include the development of smart "paints" that fix carbon dioxide into

[16] See: http://syntheticyeast.org/, accessed on 10 Jan. 2014.

inorganic carbonate, chemical agents that convert environmental waste toxins into harmless chemicals, and alternative methods of producing biofuels (Armstrong *et al.* 2012).

1.3.5 Xenobiology

31. **Xenobiology (also known as chemical synthetic biology) is the study of unusual life forms, based on biochemistry not found in nature** (Pauwels *et al.* 2012; Schmidt 2010).[17] Xenobiology aims to alter the "biochemical building blocks of life," such as by modifying genetic information to produce XNA (xeno-nucleic acids) 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, 344). 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 leaving group as well, incorporating nucleotide analogs for the leaving group, the backbone, and the nucleotide bases (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 lab over 50 unnatural amino acids that can be incorporated into a peptide (Hartman *et al.* 2007).

32. **Many hope that xenobiology will provide a way to "build-in" biosafety into synthetic biology organisms; this is still largely untested.** Xenobiology is often cited as a potential "built-in" biosafety mechanism to prevent genetic drift to wild organisms (Esvelt and Wang 2013; PCSBI 2010; RAE 2009; Schmidt 2009; Schmidt 2011; Skerker *et al.* 2009). Physical genetic material transfer might still occur, but in theory natural polymerases would be unable to accurately "read" the XNA, and thus not lead to protein production (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. By operating on an orthogonal system, the idea is that synthetic biology devices would be insulated from the rest of the cell's processes and prevent the transfer of parts resulting from synthetic biology to natural biological systems (Moe-Behrens *et al.* 2013). This claim, however, is untested as xenobiology is in an early stage of development (Pauwels *et al.* 2012). 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. 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, 20).

1.4 Current and near-term products involving synthetic biology

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

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

1.4.1 Products "for" synthetic biology

34. **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 labs that have switched to purchasing DNA from companies (Garfinkel and Friedman 2010).

35. The Registry of Standard Biological Parts hosts a collection of open source code for DNA parts following BioBrick™ standards. For amateurs and those new to synthetic biology, New England BioLabs Inc. offers the **BioBrick™ Assembly Kit**, which provides enough restriction enzymes and ligase to carry out 50 reactions for 253 USD.[18] The Kit does not contain DNA parts, but the materials to digest and combine the parts into one DNA plasmid. MIT 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 part samples as dried DNA.[19] Registered iGEM teams and lab groups can order physical samples of other parts not included in the Distribution Kit by writing to the Registry.[20]

1.4.2 Products "from" synthetic biology

36. 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 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 organisms are the result of synthetic DNA-circuits and metabolic pathway engineering; thus some of the responses to this draft document contend that some of these products are the result of "old-fashioned 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).

1.4.2.1 Production of molecules otherwise petroleum-based

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

38. Companies have started to produce **fuels such as biodiesel and isobutanol** using synthetic biology techniques. In 2010, Solazyme sold over 80,000 liters of algal-derived marine diesel and jet fuel to the U.S. Navy, and have an on-going contract with the U.S. Department of Defense for marine fuel.[21] Amyris' "Renewable Diesel," based on Biofene produced by yeast modified by synthetic biology techniques, is used by approximately 300 public transit buses in Sao Paulo and Rio de Janeiro, Brazil.[22] In 2012 Synthetic Genomics, Inc. purchased 81 acres in a "south California desert" near the Salton Sea to scale up and test algal strains in 42 open ponds (Synthetic Genomics, Inc. 2012). Calysta Energy™ converts methane and other components of natural gas into liquid hydrocarbons that can be used to make

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

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

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

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

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

fuels and chemicals. Calysta engineered the metabolic pathways of metanatrophs (methane-using bacteria), using what it describes as "synthetic biology."[23]

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

40. 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).

1.4.2.2 Production of molecules otherwise naturally-occurring

41. The commercially available and near-to-market products in this section are all 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 often 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).

42. "Major **flavor and fragrance** houses such as Givaudan, Firmenich, and International Flavors and Fragrances [IFF] are intrigued by the possibility of using biotechnology to produce key components of essential oils from abundant sugar feedstocks via fermentation," according to a 2012 article in *Chemical and Engineering News* (Bomgardner 2012). Allylix[27] and Isobionics[28] are two companies employing synthetic biology to produce synthetic bio-based versions of valencene (orange) and nootkatone (grapefruit) (Bomgardner 2012; WWICS 2012). In 2013, IFF and Swiss-based Evolva entered into pre-production phase of what they describe as "natural vanillin" from yeast-based fermentation (IFF and Evolva 2013). As of early 2014, this vanillin is anticipated to be the "first major synthetic-biology food additive to hit supermarkets" (Hayden 2014, 598). Because the vanillin is produced by a living organism (the engineered yeast) and the yeast is not present in the final product, the vanillin reportedly can be described as "natural" and does not have to be labeled in any particular way (Hayden 2014). Evolva is using similar synthetic-biology based processes in its research and development on key saffron components and stevia (WWICS 2012).[29]

43. 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

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

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

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

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

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

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

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

sourced from the livers of deep sea sharks although recently plant-based alternatives are available (ETC 2013a; WWICS 2012). In 2011, Amyris brought a synthetic biology-produced squalane[30] to the Japanese market, marketed as Neossance™ Squalane. Using Brazilian sugarcane as feedstock, Amyris transformed 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).

44. Perhaps the most famous **pharmaceutical** produced with synthetic biology is the anti-malarial semi-synthetic artemisinin; yeast was engineered to produce artemisinic acid (see section 3.2) Sanofi started production in 2013; it is as yet unclear whether the synthetic production will complement or replace the thousands of small-scale farmers of *Artemisia*, the natural source of artemisinin, in Asia and Africa (Sanofi and PATH 2013; ETC 2013a). The popular anti-influenza drug Tamiflu, which rose in importance during the swine flu pandemic, is made from shikimic acid, traditionally sourced from star anise. The ETC Group identifies the microbial fermentation process used by La Roche to produce shikimic acid as synthetic biology (ETC 2013a); Rawat *et al.* (2013, 4284) describe it as "rationale strain design by metabolic pathway engineering." Rawat *et al.* (2013) see La Roche's method as the best one yet for industrial-scale preparation of Tamiflu, but acknowledge drawbacks such as low total yield.

1.4.2.3 Industrial use of synthetic biology organisms

45. Synthetic biology is being used 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, DSM introduced and optimized two genes into a penicillin-producing microbial strain, making a process for producing the synthetic antibiotic cephalexin faster, cheaper, and less energy-intensive (Erickson *et al.* 2011). **Enzymes modified by synthetic biology techniques** are being explored and used for the production of pharmaceuticals and biofuels. For example, Januvia©, a medicine for type II diabetes, is produced by Merck using an enzyme modified by synthetic biology techniques by Codexis (BIO 2013).

1.4.2.4 Commercially available micro-organisms resulting from synthetic biology techniques

46. 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.

47. 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™[31] 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 National Institute of Standards and Technology), and ARPA-e (the US Advanced Research Projects Agency – Energy).[32]

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

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

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

1.4.2.5 Commercially available multi-cellular organisms resulting from synthetic biology techniques

48. In this category, multi-cellular organisms resulting from synthetic biology techniques are being developed for release on the market. With the exception of the Glowing Plant (described below), it does not appear that any currently on the commercial market. The prospective uses in this category are intended for environmental release.

49. **Agricultural crops** are being developed with genes modified using synthetic biology technology, intended as feedstock for biofuels. Agrivida, Inc. uses proprietary INzyme[tm] 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 (BIO 2013). This should reduce the cost and energy of breaking down feedstock for the fermentation process to produce ethanol. 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 and is an example of the lack of clear boundaries between conventional genetic engineering and "synthetic biology."[33] Similarly, Syngenta's Enogen corn contains alpha amylase enzyme in its endosperm in order to produce ethanol. The ETC Group (2013) lists it as an application of synthetic biology, but Syngenta does not use the term 'synthetic biology' is describing its design and production (Syngenta 2012).

50. **Organisms resulting from synthetic biology techniques are scheduled to be disseminated in September 2014.** In April 2013, an opportunity to invest in a "Glowing Plant" was posted on the crowd-sourcing website Kickstarter.[34] The Glowing Plant team promised to use synthetic biology techniques and software from Genome Compiler to design and "print" DNA, used to transform *Arabidopsis* to produce luciferase and luciferin. Donations of $40 USD or more were promised seeds of the Glowing Plant, to be produced using the raised funds. By the close of the Kickstarter campaign in June 2013, over $450,000 had been raised and over 8,000 people had reserved Glowing Plant seeds or plants, expected to be shipped (within the USA only) in September 2014.[35] The use of Kickstarter to fund raise and disseminate genetically-modified organisms was controversial and covered by the *New York Times*, *The Guardian*, and *Nature* (Callaway 2013; Lukacs 2013; Pollack 2013). After the close of the Glowing Plant Kickstarter campaign, Kickstarter announced revised rules; Kickstarter projects can no longer "offer genetically-modified organisms as a reward" (Dzieza 2013; Luzar 2013).[36] However, as the Glowing Plant campaign's funding was already secured when the rules were revised, plans are to ship seeds and plants as promised in September 2014. The Glowing Plant team reports that they are able to legally ship their products within the US because the designed DNA is inserted into the *Arabidopsis* genome using a gene gun (rather than using a pathogen to transform the DNA). The US Department of Agriculture (USDA) regulates plant pests, and thus actively regulates organisms modified with *Agrobacterium*, but those regulations are not triggered by organisms modified by a gene gun (Callaway 2013; Pollack 2013).[37] Antony Evans, the CEO of Glowing Plant, explained that they have communicated closely with the Environmental Protection Agency (EPA) and USDA, and will likely not have to go through a formal

[33] Also see: http://www.agrivida.com/technology/overviewtechnology.html, accessed 4 Feb. 2014.

[34] See http://www.kickstarter.com/projects/antonyevans/glowing-plants-natural-lighting-with-no-electricit, accessed 7 January 2014.

[35] Also see: http://www.glowingplant.com/, accessed 7 January 2014.

[36] See: http://www.kickstarter.com/help/guidelines, access 7 January 2014.

[37] In 2011, the USDA announced that it did not have the authority to oversee a new variety of genetically modified Kentucky bluegrass because it was transformed using gene guns rather than *Agrobacterium* (Ledford 2011).

regulated process. Evans says synthetic biology was used to produced Glowing Plant in that they used synthetic DNA and introduced longer DNA sequences encoding for complete metabolic pathways, rather than single genes (personal communication 2014). Kickstarter can no longer be used in this way, but other internet platforms exist for dissemination. Twenty bioluminescent "Starlight Avatar" plants were on auction through the internet site eBay in January 2014, available within the US.[38] While it's unclear whether synthetic biology techniques were used to produce these transplastomic plants, the Starlight Avatar sales demonstrate that internet platforms other than Kickstarter are available for such dissemination.[39]

II 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

51. **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 scales: ecosystem, species, and genetic.

52. **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 and political factors (Glowka *et al.* 1994).

53. **This section discusses the potential impacts of components, organisms and products resulting from synthetic biology techniques on the conservation and sustainable use of biodiversity.** First, a number of specific areas of current and potential applications of synthetic biology are described along with potential positive and negative impacts of these applications on the conservation and sustainable use of biodiversity. While specific hopes and concerns have been expressed in each area of research and application, there are overarching concerns around possible biosafety impacts of synthetic biology. Thus, the second part of this section examines biosafety in relation to synthetic biology, as well as possible methods of containment. Table 1 at the end of section II of this note summarizes examples of the potential positive and negative impacts of synthetic biology applications on conservation and sustainable use of biodiversity (page 33).

2.1 Applications of synthetic biology and their potential positive and negative impacts

2.1.1 Bioenergy applications of synthetic biology

54. **Bioenergy applications, particularly through fuel production, are a significant focus of synthetic biology research** (WWICS 2013a). As discussed above (section 1.4.2.1), 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

[38] See: http://www.ebay.com/cln/bioglow/Bioglow-Auction/76766769010, accessed 11 Feb. 2014.

[39] The Starlight Avatar plants by Bioglow have been described as resulting from "synthetic biology processes" in some press (See http://www.dezeen.com/2014/01/13/worlds-first-glow-in-the-dark-plant-genetically-engineered/, accessed 23 Feb. 2014), but the company does not use this term to describe its technology (See: http://bioglowtech.com, accessed 23 Feb. 2014).

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 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 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).

55. **There could be significant benefits for biodiversity from replacing fossil fuel energy sources with bioenergy.** At a significant scale, these approaches could reduce global dependence on fossil fuels and cut harmful emissions (PCSBI 2010). Through the CBD's cross-cutting programme on "climate change and biodiversity," CBD bodies have documented and assessed the interlinkages of the two areas.[40] 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).

56. **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, 1). Much synthetic biology research is on designing organisms that will use biomass as feedstock to produce fuels, chemicals, and pharmaceuticals (PCSBI 2010). 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 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 potential lost ecological functions of biomass in soil, there is also concern around the social impacts of increased biomass removal. Some civil society groups are concerned that, in part due to increased demand from synthetic biology, the tropics and sub-tropics will be targeted for their biomass and lead to economic and environmental 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, 63).

57. **As discussed in more detail later (section 2.2), 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).

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

2.1.2 Environmental applications of synthetic biology

58. **Another area of synthetic biology research is in environmental applications, most of which would require contained use outside of the laboratory or environmental release of organisms resulting from synthetic biology techniques.** Sinha *et al.* (2010) "reprogrammed" *E. coli* to both increase movement in the presence of atrazine and degrade the herbicide. Although this work does not yet translate outside of a laboratory setting, it is seen as a step towards producing a microbe for *pollution control and remediation* that would break down once it has degraded its target toxin, not further altering the microbial environment (Kirby 2010; Singha *et al.* 2010). Scientists also 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 & 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 changed color in the presence of arsenic. They have founded a start-up company, Lumin Sensors, to develop a working device (French *et al.* 2011; WWICS 2013b). The 2011 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.[41]

59. **The use of engineered micro-organisms for bioremediation and other environmental applications "has been a holy grail" - much desired but constantly out of reach - since recombinant DNA technology was first introduced** (Skerker *et al.* 2009). Since the 1980s, genetically engineered strains of micro-organisms have failed to survive in indigenous microbial communities (Skerker *et al.* 2009, Lorenzo 2010; Wright *et al.* 2013). The failures of genetically-modified micro-organisms are understood differently by different communities. Microbial ecologists and environmental NGOs understand the failure to be due to the unpredictable complexity of natural microbial ecosystems. Synthetic biologists rather see the previous failures as due to the lack of sophistication of conventional genetic engineering (Marris and Jefferson 2013). As a result, synthetic biologists are generally optimistic about the potential for synthetic biology to succeed where previous modified micro-organisms for environmental release have failed (Garfinkel and Friedman 2012; PCSBI 2010; Schmidt and de Lorenzo 2012; Skerker *et al.* 2009). If so, synthetic biology could provide less toxic and more effective tools for bioremediation, which would positively impact local biodiversity.

60. **If synthetic biology succeeds in producing microbes sufficiently hardy for release into the environment, such microbes would potentially raise significant challenges for biosafety in their survival and persistence** (König *et al.* 2013) (section 2.2 on biosafety). The WWICS Synthetic Biology Project has 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 in 200, 2011, and June and December of 2012). One question is how an organism designed for environmental release can be robust enough to accomplish its intended task but not then 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 in 'building-in' biosafety (PCSBI 2010; Schmidt and de Lorenzo 2012; Skerker *et al.* 2009).

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[41] 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.

2.1.3 Wildlife-targeted applications of synthetic biology

61. **Synthetic biology techniques are being explored for their utility in conservation efforts.** 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.[42] Redford *et al.* (2013) suggest that synthetic biology applications in agriculture and bioenergy could alleviate pressure on ecosystems, aiding conservation. 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 target disease vectors such as mosquitoes by introducing transgenic individuals into a wild population. While it's unclear whether synthetic biology techniques were used by Oxitec to produce the transgenic mosquitoes field tested in the Grand Cayman to control dengue fever carriers (Subbaraman 2011), synthetic biologists have pointed to the potential for synthetic biology to design the synthetic genetic circuits that such a system would disseminate (Weber & Fussenegger 2012). Researchers have introduced a synthetic homing endonuclease-based gene drive system into mosquitoes in the lab, which could be used to increase the transmission of genetic modifications to wild populations of mosquitoes (Windbichler *et al.* 2011). Such potential uses of synthetic biology could have positive impacts on the health of humans, wildlife and ecosystems. There would also be biosafety considerations relating to the use of organisms resulting from synthetic biology techniques designed for environmental release (section 2.2).

62. **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 biotechnology.** De-extinction was the subject of a day-long TEDx conference in Washington, DC (USA) co-organized by the Long Now Foundation and National Geographic, and was *National Geographic* magazine's March 2013 cover story.[43] 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 for adapting the genomes of existing species to produce the physiological traits of extinct species, such as tusks and woolly hair (Church 2013). Although "de-extinction" hasn't yet been achieved beyond viruses, conservationists and synthetic biology scientists are starting to discuss the potential impacts on biodiversity and ecosystems.

63. **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

[42] 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.

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

"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).

64. **The use of synthetic biology for de-extinction projects and "conservation" projects more broadly also raises some concerns.** As discussed more fully in section 2.2, there is the possibility of direct impacts on biodiversity, such as organisms resulting from synthetic biology techniques becoming invasive.[44] There is also concern about indirect impacts of the promises of synthetic biology and de-extinction. A prominent concern among conservationists is that the hunt for synthetic biology solutions will divert significant funds and other resources from other conservation efforts (Ehrenfeld 2013; Ehrlich 2014; Pimm 2013; Temple 2013). The editors of *Scientific American* warn that de-extinction "threatens to divert attention from the modern biodiversity crisis" (Editors, 2013). Stuart Pimm points out that his work with poor people in Brazil and Madagascar does not generate money for his university, unlike that of molecular biologists, and that de-extinction "can only perpetuate" the trend of university de-investment in ecology and field biology while "seduc(ing) granting agencies and university deans into thinking they are saving the world" (Pimm 2013). These concerns about diversion of resources from other conservation efforts are particularly keen because of the speculative nature of de-extinction projects and their high price tags (Ehrenfeld 2013; Ehrlich 2014). In comments to an earlier draft of this document, one organization noted that, outside of synthetic biology and conservation communities, publicity around de-extinction has prompted research policy communities to consider responsible conduct of research and prioritization of research areas. Another concern is that support for *in situ* conservation may decrease with the expectation that "lost" species will be able to 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.

2.1.4 Agricultural applications of synthetic biology

65. **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* says: "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, 26). In 10 years, the RAE (2009, 7) anticipates the use of synthetic biology 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). These comments are all about *potential* applications of synthetic biology to agriculture; thus far, it is unclear whether there are commercialized agricultural applications of synthetic biology. As discussed previously (section 1.4.2.5), 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 enzyme sequences are "synthetic biology" appears to be a point of contention (BIO 2013; Lipp 2008; Schmidt 2012).

[44] 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, 9).

66. **The potential for synthetic biology in agriculture could lead to positive impacts for biodiversity.** The use of synthetic biology in agricultural production sectors might foster ‘‘sustainable intensification’’ and thus ‘‘land sparing’’ to reduce land conversion and increase protection of wild habitats (Redford *et al.* 2013). There are hopes that synthetic biology can be used to design plant feedstocks or micro-organisms that would need less chemical pesticides and fertilizers, which could have positive ecological impacts (PCSBI 2010).

67. **Possible applications of synthetic biology for agriculture could lead to negative impacts for 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 2.2 this could lead to the possibility of negative impacts at an ecological level (such as organisms resulting from synthetic biology techniques becoming invasive or disrupting food webs) or through the transfer of DNA from sexual gene flow or horizontal gene transfer (König *et al.* 2013; Wright *et al.* 2013).

2.1.5 Applications of synthetic biology to replace natural materials

68. **Synthetic metabolic engineering and DNA-based device construction are being used to produce chemicals and molecules that are otherwise sourced from wild and agriculturally-produced plants and animals.** Groups from industry and civil society have pointed to potential positive and negative impacts on biodiversity. Applications that are on or near market mostly are the result of synthetic metabolic pathway engineering, and therefore are not universally recognized as resulting from synthetic biology techniques. 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 2.2).

69. **Molecules produced through synthetic biology could enable conservation of plants and animals 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 from sharks. Unilever has already replaced shark squalene with plant-based in response to a campaign by Oceana to preserve deep sea sharks.[45] Companies point to the price volatility and limited availability of olive-sourced squalene, however, and non-European manufacturers in particular have continued to use deep sea sharks, according to a French NGO (BLOOM 2012; Centerchem undated). In 2011, Amyris brought a synthetic biology-produced squalene[46] to the Japanese market, marketed as Neossance™ Squalane. 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.

70. **Synthetic biology products could displace products that are key to *in-situ* conservation projects.** For example, Evolva and International Flavors and Fragrances, Inc. are in pre-production for “natural vanillin” produced through synthetic biology techniques, described as a “cost-effective, natural and sustainable” source for a “volatile raw material” (IFF and Evolva 2013). They plan to market the product as “natural” in the EU, and hope to have a competitive advantage over other synthetic (i.e.,

[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.

chemical) vanillin.[47] ETC Group warns that this 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 2.1.1 (ETC 2013b). Related to this, ETC Group questions whether a switch from monoculture oil palm plantations to monoculture sugar plantations (for feedstock for synthetic biology processes) is an improvement for biodiversity (ETC 2013a).

2.1.6 Applications of synthetic biology for chemical products

71. **A significant potential use of synthetic biology is in "white" biotechnology, 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).

72. **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, 276). 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, 52; 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 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 carcinogens and eutrophication than fossil-based polymers.

2.2 Biosafety concerns and approaches to containment

73. In the context of synthetic biology, issues related to "biosafety" are frequently raised, often to describe measures designed to mitigate or avoid unintended negative impacts on biodiversity. This section first examines biosafety concerns commonly raised relating to synthetic biology, and then examines strategies for containment of organisms resulting from synthetic biology techniques, both for contained use and those intended for environmental release.

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[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". Several products that were previously sold as "natural" can no longer use that label." Available at: http://www.evolva.com/products/vanilla, accessed on 21 March 2013.

[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, 8).

2.2.1 Types of potential impacts related to biosafety

74. This section focuses on biosafety concerns related to the accidental or intentional release of organisms resulting from synthetic biology techniques: ecosystem-level impacts; genetic transfer; and unexpected properties.

2.2.1.1 Ecosystem-level impacts

75. **Unintentional or intentional release of organisms resulting from synthetic biology techniques to ecosystems outside of a contained lab or production facility could negatively impact biodiversity.** One set of concerns is around the possibility of the survival and persistance of such organisms. For example, organisms resulting from synthetic biology techniques could displace existing species because of engineered fitness advantages 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, through an algal bloom of an escaped algae engineered for biofuel production (Redford *et al.* 2013; Snow and Smith 2012; Wright *et al.* 2013).

76. **Within scientific and policy communities, there is disagreement over the degree and probability of harm that organisms resulting from synthetic biology techniques *intended for contained use* could cause if released (Dana *et al.* 2012; Lorenzo 2010; RAE 2009; Snow 2011; Snow & Smith 2012; Tait & Castle 2012; Zhang *et al.* 2011).** A common argument is that an accidental release of synthetic biology organisms engineered for contained use would most likely *not* lead to survival and propagation because engineered changes generally lead to reduced fitness (Garfinkel and Friedman 2010; Lorenzo 2010; RAE 2009). Speaking about engineered algae for bioenergy, Margaret Mellon of the Union of Concerned Scientists said she would not "lose sleep" over its escape (Pollack 2010). Ecologists Alison Snow and Val. H. Smith, on the other hand, point out that the majority of research in synthetic biology uses microbes as hosts, and that microbes have a particularly high potential for "rapid evoluationary change" (Snow and Smith 2012; Snow 2011). Snow notes that novel microbes resulting from synthetic biology techniques that seem innocuous or weak might survive due to mutations (Snow 2011). 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).[49]

77. **Organisms resulting from synthetic biology techniques *intended for environmental release* may present additional complexities and types of possible negative impacts.** 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). Many synthetic biologists are aiming to design *micro-organisms* that are sufficiently hardy for release into the environment (section 2.1.2). Belgium's Biosafety and Biotechnology Unit notes that "risk assessors and regulators have relatively little experience considering the potential risks posed by the intentional release of micro-organisms," and that environmental microbiology is more complex (Pauwels *et al.* 2012, 31). 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, 31). Rodemeyer, writing for the WWICS Synthetic Biology Project, also notes that regulatory agencies have had "relatively little experience considering the potential risks posed by the eventual evolution of genetically

[49] In comments on the draft version, one organization pointed out that the food and beverage sector has used and modified yeasts and bacteria for 10,000 years without those organisms invading the natural environment. They also point to a 2001 peer-review publication by Novozymes A/S on the use of inactivated genetically modified micro-organisms as agricultural fertilizer; they found that the presence of antibiotic resistance genes in the inactivated sludge did not lead to changes in the soil bacteria profile compared to other soils (Andersen *et al.* 2001).

engineered microorganisms intended for non-contained use"; as most GMOs have been annual food crops, evolution has not been seen as a relevant potential risk factor (Rodemeyer 2009, 26).

2.2.1.2 Transfer of DNA

78. **Altered DNA could be transferred from organisms resulting from synthetic biology techniques to other organisms, either by sexual gene flow or by horizontal gene transfer.** Sexual gene flow occurs when genes from one organism are sexually passed on to unaltered populations of the same species or a related species (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). It can also happen through seed exchange. An example from the past decades of use of genetically engineered crops is the unintended survival and dispersal of transgenes among maize in Mexico, which appears to have been facilitated by formal and informal seed systems and grain markets (Dyer *et al.* 2009; Schmidt and Lorenzo 2012). 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 known to 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 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 dies (Wright *et al.* 2013).

79. **The transfer of genetic material from an organism resulting from synthetic biology techniques to another organism would change biodiversity at a genetic level (genotype) and could spread undesirable traits (phenotype).** Some scientists, commentators, and civil society groups have expressed concern that the spread of novel DNA could result in undesirable traits in other organisms, such as antibiotic resistance (a common marker in synthetic biology and genetic engineering more broadly) or the production of enzymes to 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 a harm (Marris and Jefferson 2013). 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 doesn't consider the transfer of genetic material as an adverse effect itself, but a potential mechanism by which adverse effects could occur.

2.2.1.3 Emergence of unpredictable properties

80. **The scientific community recognizes that synthetic biology could result in radically different forms of life, with "unpredictable and emergent properties" (RAE 2009, 43; Garfinkel and Friedman 2010; Mukunda *et al.* 2009).** However, there is not 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 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" (2012, 2201). In the same article, however, Schmidt and de Lorenzo (2012) explain that they are hopeful that xenobiology will provide Certainty of Containment. Dana *et al.* reflect a concern for the "unknown unknowns" of synthetic biology in their call for significantly increased funding for

dedicated synthetic biology risk research: "No one yet understands the risks that synthetic organisms pose to the environment, what kinds of information are needed to support rigorous assessments, or who should collect such data" (Dana *et al.* 2012, 29).

81. **In discussions of the danger of unforeseen results in synthetic biology, a common example is an experiment in 2000 using conventional 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 Jackson and Ramshaw 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).

82. **There is disagreement over the adequacy of existing risk research and the application of conventional GMO risk assessment methodologies to organisms resulting from synthetic biology techniques .** 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 natural and synthetic organisms; 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. Joyce Tait and David Castle, writing from the UK ESRC Innovation Centre, responded that the investment proposed by Dana *et al.* was "not yet justified" (Tait and Castle 2012) They also said that "The questions raised by Dana *et al.* should be considered as part of any risk-governance system for synthetic biology" (Tait and Castle 2012, 37). Their disagreement thus seems to be around the scale of dedicated risk research, and not the content. Synthetic biologist Victor de Lorenzo argues that the results of current synthetic biology research and commercialization (ie, not yet orthogonal systems such as xenobiology) are sufficiently "familiar" that risk assessment checklists for conventional GMOs are still appropriate (de Lorenzo 2010). [50]

83. **Perspectives on the adequacy of risk assessments and regulatory structures designed for conventional GMOs in addressing synthetic biology depend in part on views of the novelty of current synthetic biology techniques compared to conventional genetic engineering.** 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, 24-25). 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

[50] For more on the coverage of synthetic biology by national and regional risk assessment processes, see the document on *Synthetic biology: possible gaps and overlaps with the applicable provisions of the Convention and its Protocols* (UNEP/CBD/SBSTTA/18/INF/4).

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), the capacity for synthetic biology techniques *already* demand new risk assessment procedures and regulatory responses. The ICSWGSB (2011) argue that, as current risk assessment protocols rely on an assessment of the risks of the "parental organism," this is inadequate for organisms produced using synthetic biology techniques that have no analog in the natural world.

84. **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 scientific uncertainty can be described as uncertainty (when the types of harm can be identified, but not their probabilities), ambiguity (where the measurement or meanings of the kinds of harm are contested), and ignorance (where neither the outcomes nor probabilities can be characterized) (Wynne 1992; Stirling 2010). Zhang *et al.* (2011) warn that, as with other emerging technologies, there has been a tendency among governments to respond to synthetic biology as if it represents only identifiable and measurable "risks." Zhang *et al.* (2011) recommend meaningful engagement with the other aspects of uncertainty endemic to synthetic biology, for example, by identifying "orientational" questions to provoke reflexiveness.

2.2.2 Strategies for containment

85. Containment strategies to prevent unintentional release or exposure of organisms resulting from synthetic biology techniques are physical (barriers to entering the environment) and biological (inhibited ability to reproduce or survive outside of contained system) (Schmidt and Lorenzo 2012).[51] Biological strategies are also being explored to contain the impacts of organisms resulting from synthetic biology techniques designed for environmental release. Containment systems occur within social and institutional systems; it is also important to consider the conditions of use and characteristics of the users of synthetic biology technologies (Marris and Jefferson 2013). Research involving recombinant or synthetic nucleic acid that is funded by the US National Institutes of Health (NIH) must follow the NIH's "Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules," which includes conditions for physical and biological containment (NIH 2013).

2.2.2.1 Physical containment

86. **Physical containment systems put in place physical barriers and institutional practices to prevent accidental escape or exposure of organisms.** Formal research laboratories are categorized by Biological Safety Levels (BSL) 1-4, from basic to maximum containment following the World Health Organization's standards (WHO 2004). BSL correspond to certain codes of practice and the presence of laboratory design and facilities (*Ibid.*). Current industrial use of organisms produced by synthetic biology techniques are in closed settings, such as bioreactors (Moe-Behrens *et al.* 2013). The UK Healthy and Safety Laboratory noted that research and production under conditions of contained use can be used to develop evidence on how to regulate future applications of synthetic biology that would involve deliberate release, in a step-by-step approach (Bailey *et al.* 2012). Future uses of synthetic biology could straddle the line between containment and release. For example, French *et al.* (2011) consider their prospective biosensor for arsenic for use in a contained device - but outside of a laboratory - as different than biosensors designed to be exposed directly to the environment. Also, organisms may have different likelihoods of accidental environmental release because of their need for exposure to sunlight and carbon dioxide, such as algae grown in open ponds (WWICS 2013).

[51] The civil society coalition that published *Principles for the Oversight of Synthetic Biology* (FOE *et al.* 2012) also calls for geographic containment (lab locations where organisms could not survive the surrounding environment) as part of a wider set of containment measures.

87. **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).** One of the conclusions that Schmidt and de Lorenzo 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" (Schmidt and de Lorenzo 2012, 2200). Synthetic biologists Wright *et al.* call it "prudent" to include some form of physical containment, but caution that: "Failure in this case is a matter of when, not if" (Wright *et al.* 2013, 5). The disagreement is thus largely not about whether engineered organisms will escape physical containment; rather it is over the degree of concern this should elicit and the appropriate responses.

88. **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 labs (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, 6). They do not specify a specific Biosafety Level, but more generally call for physical, geographical and biological confinement strategies that prevent the release of synthetic organisms into the biosphere (*Ibid.*, 7). Tucker and Zilinskas, experts in nonproliferation policy, declared that "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 3 or even 4) until their safety could be demonstrated in a definitive manner" (Tucker and Zilinskas 2006, 34).[52] 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. 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, 80).

2.2.2.2 Biological containment

89. In reference to needs 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, 43; Marlière 2009; Moe-Behrens *et al.* 2013; PCSBI 2010; Wright *et al.* 2013).** There are four general categories of ideas for built-in biosafety: kill-switches; horizontal gene transfer prevention; trophic containment; and semantic containment.

90. **The idea of engineered induced lethality (also referred to as a "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 the possibility of "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, 130). This is also a popular suggestion among iGEM teams as a way to

[52] In their comments to this draft, the J. Craig Venter Institute pointed out that the years of iGEM competitions without adverse outcomes argues against the idea that BSL-3 or -4 conditions would be necessary for SB. They also asked *how* safety could be "demonstrated in a definitive manner."

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. Some number of microbes always spontaneously mutate and deactivate the lethal gene. Wright *et al.* do not see this area of research succeeding: "dependency devices based solely on toxins seem designed for failure due to their inability to withstand mutation over time" (Wright *et al.* 2013, 7).

91. **Trophic containment is another suggested biological barrier; organisms are designed to be unable to synthesize an essential compound 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 selection. The compound required for survival might be available in the environment to which it escapes (Moe-Behrens *et al.* 2013). Even if the compound isn't environmentally present, cells might parasitically rely on metabolites from certain kinds of neighbouring organisms, or gene transfer could compensate for the mutation (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, 5.4).[53] A related method of containment is being explored in influenza research. Influenza viruses have been engineered to complement species-specific micro-RNA; this was found to attenuate influenza pathogenicity in different species (Langlois *et al.* 2013). It is hoped that this could add extra precaution in studying pathogens from other species (Devitt 2013).

92. **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) display 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).

93. **Semantic containment would require creating organisms that "cannot communicate with the extant biochemistry of the existing live world" (Schmidt and Lorenzo 2012, 2201).** Xenobiology is the main area of research exploring the creation of orthogonal biological systems. By producing genetic material with additional nucleotides (with the bases ATGCPZ, for example) or an alternate backbone other than ribose or deoxyribose, a cellular information system may be created that has the same outputs as other cells but cannot be "read" by natural polymerases (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, 10), 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).

94. **According to Wright *et al.* (2013, 1222), "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 (Wright *et al.* 2013).

[53] It should be noted that Moe-Behrens *et al.* (2013) cites studies no later than 2006, and many from the 1990s.

95. **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, 6). These groups are responding to what they perceive as overly-optimistic expectations of many synthetic biology commentators for the promise of built-in biosafety.

2.2.2.3 Social aspects of containment

96. **The effectiveness and form of containment systems 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.

97. **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 laboratory potentially have 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, 11). 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). Since 2008, iGEM contestants have had to answer biosafety questions. In their submission to the CBD Secretariat, EcoNexus criticized the iGEM biosafety process (as of 2011): "Leaving the assessment of synthetic genetically modified organisms to undergraduates answering three or four questions, is by no means a sufficient risk assessment" (EcoNexus 2011, 12). Currently, iGEM requires all project teams to fill out a four page Basic Safety Form, including questions about whether the biological materials used pose risks to safety and health of the team or general public, the environment, or security.[54] If a project team uses an organism, or a part from an organism, that is rated above Risk Group 1 or uses mammalian cells or parts, the team must complete Part 2 of the Biosafety form, which asks about the use of the organism or part, how it was physically acquired, potential health/safety risks, and the measures the team intends to take to ensure the project is safe. If the organism or part is listed under the Australia Group guidelines on "transfers of sensitive chemical and biological items" or otherwise restricted for transport, the team is asked how it will ship the part to iGEM and the Jamboree.[55]

98. **Some synthetic biology is being practiced by amateur biologists, sometimes referred to as "garage hackers" or the "DIYbio" (do-it-yourself biology) community (Ledford 2010; Schmidt 2009; Guan *et al.* 2013).** There is contention over how many people are engaging in 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 (EcoNexus 2011; FOE 2010). In January 2013, the Woodrow Wilson International

[54] See http://2013.igem.org/Safety, accessed 16 Jan. 2014.

[55] See http://igem.org/wiki/images/7/71/IGEM_Biosafety_Form_Part_2.pdf, accessed 16 Jan. 2014.

Center for Scholar's (WWICS) Synthetic Biology Project together with DIYbio.org launched an "Ask a Biosafety Expert" webpage. Thus far, the "Ask a Biosafety Expert" committee has responded to inquiries ranging from how to prevent transformed plant material from leaving a lab, the potential safety hazards of working with a gene gun, the safety of working with nitrogen gas in a small lab, and what kinds of labs are required to be CLIA certified.[56] The WWICS Synthetic Biology Project released a 2013 report on the status and "myths" of DIYbio, based on a survey of primarily the DIYbio North American community (Grushkin *et al.* 2013). Based on the results of the survey, WWICS found that most DIYers work with BSL 1 organisms on relatively unsophisticated projects, and that they present a "low" risk to the environment either from release of their modified organisms (because they are BSL 1) or from the disposal of their lab waste (Grushkin *et al.* 2013, 18). As with other risks the DIYbio may pose, WWICS suggests that these risks be reassessed as synthetic biology technology and the DIY community develops (Grushkin *et al.* 2013).

99. **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's 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).

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

[56] See http://ask.diybio.org/questions/, accessed 26 Feb. 2013.

	communities (ETC 2010; FOE *et al.* 2012; FOE 2010) If synthetic biology techniques open up new sources of energy such as algae and seaweed, increased demand may encroach on traditional uses (ETC 2013) Biosafety considerations for accidental release of organisms resulting from synthetic biology techniques (section 2.2)
Environmental applications of synthetic biology	Micro-organisms resulting from synthetic biology techniques may make more effective and 'green' pollution control and remediation (Kirby 2010; Singha *et al.* 2010) Micro-organisms resulting from synthetic biology techniques may work as biosensors, helping to identify areas contaminated with specific pollutants (French *et al.* 2011)
	Biosafety considerations around the deliberate release of micro-organisms resulting from synthetic biology techniques (section 2.2)
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) Synthetic biology techniques may be used to target threats to wildlife, such as disease vectors (Weber & Fussenegger 2012)
	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) Biosafety considerations around the deliberate release of organisms resulting from synthetic biology techniques (section 2.2)
Agricultural applications of synthetic biology	The potential for synthetic organisms 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). 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)
	Biosafety considerations around the deliberate release of organisms resulting from synthetic biology techniques (section 2.2)
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) Biosafety considerations around accidental release of micro-organisms resulting from synthetic biology techniques (section 2.2)
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) Biosafety considerations around accidental release of micro-organisms resulting from synthetic biology techniques (section 2.2)

III ADDITIONAL RELEVANT INFORMATION ON COMPONENTS, ORGANISMS AND PRODUCTS RESULTING FROM SYNTHETIC BIOLOGY TECHNIQUES THAT MAY HAVE IMPACTS ON ASSOCIATED SOCIAL, ECONOMIC AND CULTURAL CONSIDERATIONS

100. This section discusses potential positive and negative impacts of components, organisms and products resulting from synthetic biology with regard to social, economic and cultural considerations. Table 2 at the end of this section summarizes examples of potential positive and negative impacts (page 46).

3.1 Biosecurity considerations relating to biodiversity

101. **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, 71).** Synthetic biology presents potential challenges to biosecurity, as well as potential tools to aid in security efforts.

102. **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).[57] 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, 11).

103. **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, 3).** 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.

104. **Infectious viruses have been created using what some consider to be synthetic biology techniques; it is predicted that bacterial pathogens will 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 lab in 2002, using oligonucleotides ordered from a commercial supplier (Cello *et al.* 2002).[58] 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, 8). 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, 15) 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.

105. **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, 71). Synthetic biologist

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

[58] 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.

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

3.1.1 Potential pathways for biosecurity threats

106. **Some scholars predict that "the 'fruits' of synthetic biology will be first abused in a state-level program" (Kelle 2009, 86; Mukunda *et al.* 2009; Schmidt *et al.* 2009).** Although much of the attention is on the threat of non-state actors, scholars point to the history of States applying advances in the life sciences to biological weapons and the high technological hurdles to producing pathogens with synthetic biology. Mukunda *et al.* (2009) anticipate a spiral dynamic in which defensive government synthetic biology research is interpreted as offensive by other governments, leading them to commit more defense spending in response, creating a synthetic-biology arms race. Government-led synthetic biology research into biological weapons also provides opportunities for individuals to gain access to dangerous materials (Garrett 2013). The 2001 attacks of mailed letters containing anthrax were made by an employee of the US Army, working in Biosafety Level 3 and 4 labs (Garrett 2013; Wilson 2013).

107. **Currently, using synthetic biology to produce pathogens is not an easily accessible route for independent bioterrorists.** Synthetic biologist James Collins often employs the analogy that assembling a living cell from a list of genes is "like assembling a jumbo jet from a list of mechanical parts" (Collins 2012, S10; Various 2010). Also, intentionally creating virulent organisms remains extremely difficult; sequence-based prediction of virulence is not yet possible (de Lorenzo 2010; Relman 2010). Furthermore, once DNA of a pathogen is produced, it still must be weaponized and disseminated (Douglas and Savulescu 2010).

108. **Advances in synthetic biology knowledge and tools may significantly lower barriers to its use by bioterrorists.** One of the goals of synthetic biology is to make biology easier to engineer, transforming it from a craft requiring tacit knowledge ("procedural and substantive knowledge primarily gained from experience instead of formal education") to an industrial process (Mukunda *et al.* 2009, 14). Mukunda *et al.* consider the need for tacit knowledge to be one of the "most significant barriers to bioweapon proliferation," and thus synthetic biology is "likely to eventually expand the universe of capabilities open to its most skilled practitioners" (Mukunda *et al.* 2009, 14-15). Commercial DNA synthesis companies are continually improving on the cost and speed, and most labs are transitioning from making their own oligonucleotides to ordering from companies. Although this trend is leading to the consolidation of DNA synthesis, it has been accompanied by labs posting their old DNA synthesis machines for sale over the internet (Garfinkel and Friedman 2010). These unregistered machines pose a possible pathway for the production of DNA of pathogens, although, again, there are currently much easier and cheaper methods to procure pathogens (Garfinkel and Friedman 2010).

109. **Synthetic biology is often described as presenting the problem of "dual use," where research for benign purposes can be directly misapplied and used as a threat (Garfinkel *et al.* 2007; Douglas and Savulescu 2010; Nuffield 2012; PCSBI 2010).** This tends to lead to technical discussions on the difficulty of misapplications (*e.g.:* PCSBI 2010). Bennett *et al.,* writing from the Synthetic Biology Engineering Research Center (Synberc) at UC Berkeley, argue that this "dual use" framing sets up a dichotomy of good and bad uses and users that "overly simplifies the moral landscape" and fails to address the problem at hand: dangerous events, whether intentional or accidental (Bennett *et al.* 2009, 1110).

3.1.2 Responses to biosecurity concerns

110. **Commercial DNA synthesis companies voluntarily screen DNA sequences and customers.** As early as 2004, prominent synthetic biologist George Church's "Synthetic Biohazard Non-Proliferation

Proposal" recommended that synthesis instruments and reagents be licensed and DNA sequences screened for select agents (Church 2004). At present, no States have passed mandatory licensing or screening regulations. The US Department of Health and Human Services' voluntary *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* recommends that commercial DNA synthesis firms screen customers and "sequences of concern" (US DHHS 2010). Since 2009, two corporate DNA synthesis consortia have agreed to separate but similar protocols, including sequence screening for pathogens, record keeping, and customer screening for legitimacy (IASB 2009; IGSC 2009).[59]

111. **There are acknowledged gaps in commercial DNA synthesis screening arrangements.** Not all US or European synthesis companies have signed on to the IGSC Protocol or IASB Code, and there are no consortium member companies from China, although several leading global suppliers are Chinese (Tucker 2010; Terrill and Wagner 2010).[60] In 2010 representatives of IGSC estimated that 20% of commercial DNA synthesis companies were outside of the consortium (Terrill and Wagner 2010). Mukunda *et al.* describe the large-scale centralized synthesis of DNA as a "choke point" that requires international agreement to prevent a leaky system (Mukunda *et al.* 2009, 18). Also, this biosecurity measure can be avoided by ordering short DNA sequences (oligonucleotides) from companies instead of long ones. Researchers constructed the polio virus using commercial-synthesized oligonucleotides (although it should be noted that, as polio is not on any select agent lists in the US, longer sequences would not have have triggered alerts) (Cello *et al.* 2002; Garfinkel and Friedman 2010). Furthermore, there is debate as to whether pathogenic DNA sequences can be clearly identified, as scientists often cannot predict virulence, and expressions of DNA sequences depend on context and environment (Relman 2010). Bennett *et al.* argue that technological responses are inadequate responses to the complex global landscape, in which lines between good and bad users and uses are constantly shifting (Bennett *et al.* 2012).

112. **The BioBrick™ Foundation's approach to biosecurity relies on openness and transparency rather than restricting technologies to specific communities.** The BioBrick™ Public Agreement states that the user will "refrain from using the Materials in connection with any intentionally harmful, negligent, or unsafe uses."[61] Beyond this contractual agreement between a BioBrick™ User and Contributor, there is no oversight by the Foundation into the specific uses of BioBrick™ parts. The openness of this model of synthetic biology is intended to provide a "distributed network of many practitioners bound to notice and report malfeasance" (Torrance 2010, 662).

3.2 Economic considerations relating to biodiversity

113. **The global market for synthetic biology products is growing rapidly, as are investments in synthetic biology research.** Market forecasters BCC Research estimate the 2010 global synthetic biology market at $1.1 billion and predict it will reach $10.8 billion by 2016.[62] While these numbers are 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

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[59] The International Association Synthetic Biology (IASB), based in Germany, has a *Code of Conduct for Best Practices in Gene Synthesis* (IASB 2009). The International Gene Synthesis Consortium (IGSC), based in the USA, has a *Harmonized Screening Protocol* (IGSC 2009). The content of these guidelines are similar, but the processes by which they were developed differ; the IASB code was openly drafted, while the IGSC protocol was written by a small group "limited to suppliers with the largest market share" (Tucker 2010). Although the current drafts are almost identical, this difference in procedure may lead to divergences in future drafts (*Ibid.*).

[60] According to the International Council for the Life Sciences, members of the Chinese Academy of Sciences and a leading Chinese gene foundry have called for developing a Chinese Synthetic Biology Association and a Chinese Code of Conduct, working with ICLS. Available at: http://iclscharter.org/our-work/synthetic-biology/, accessed on 22 April 2013.

[61] See https://biobricks.org/bpa/users/agreement/. Accessed on 3 May 2013.

[62] See *Synthetic Biology: Emerging Global Markets*, at http://www.bccresearch.com/report/global-synthetic-biology-markets-bio066b.html. Accessed on 17 April 2013. An indication of the money related to SB is the cost of BCC Research's report: $5450 for a single user license, up to $9350 for an enterprise license.

18.7%.[63] The WWICS Synthetic Biology Project estimates that the US and European governments funded over a half billion USD in synthetic biology research from 2005 to 2010 (WWICS 2010).

114. **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 "a bioeconomy" as **"**a world where biotechnology contributes to a significant share of economic output." (OECD 2009, 8). 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, 1). 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, 1).[64] Civil society groups' definitions of the bioeconomy are similar to that of the European Commission.[65] 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, 2). 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, 5).

115. **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, 15). 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).

116. **State-led policies and strategies are driven by the anticipated benefits of an expanded global bioeconomy**. The EC is pursuing the bioeconomy to "reconcil(e) demands for sustainable agriculture and fisheries, food security, and the sustainable use of renewable biological resources for industrial purposes, while ensuring biodiversity and environmental protection" (EC 2012a, 1). The EC 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, 1). Brazil is aligning its strategies to become the "No.1 Global Bioeconomy," building on its natural resources base and extensive biodiversity.[66] And States that have not yet developed bioeconomy-specific strategies are adopting the

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

[64] 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, fn 3).

[65] 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, 16).

66 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.

language of the bioeconomy, such as the Malaysian Minister of Natural Resource and Environment identifying "bio-economy" as key to transforming Malaysia into a high income country.[67]

117. **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 2.1.1, 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, 6). 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, 15; ICSWGSB 2011; Hall 2012).

118. **Many of the first wave synthetic biology commercial applications replicate naturally-occurring molecules that are expensive or difficult to source outside the lab or produce in the lab 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.

119. **"Semi-synthetic artemisinin," an anti-malarial drug, 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 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 a yeast using 12 new synthetic genetic sequences to produce high levels of artemisinic acid (Ro *et al.* 2006). OneWorldHealth, Amyris (a commercial synthetic biology company co-founded by Keasling), and pharmaceutical company Sanofi partnered to produce semi-synthetic artemisinin. The term "semi-synthetic" is used because Sanofi has developed a proprietary photochemical method to convert artemisinic acid into artemisinin (Sanders 2013). In 2013, Sanofi announced the launch of large-scale production upon regulatory approval, with plans to produce 35 tons of artemisinin that year and 50 to 60 tons by 2014, the equivalent of 80-150 million ACT treatments (Sanofi and PATH 2013). Thus far, Sanofi has exported approximately 400kg of semi-synthetic artemisinin to India, the bulk in one shipment for 350USD/kg.[68]

120. **There are significant 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,

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

[68] See: http://www.infodriveindia.com/, accessed 21 Feb. 2014.

10; PCSBI 2010; RAE 2009).[69] Because production by Sanofi and PATH 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).

121. **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; personal commun. Charles Giblain[70] 2014). 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 350 and 400USD, and that the semi-synthetic product would act as a price regulator.[71] But, at an April 2013 conference on synthetic biology and conservation, Keasling said "moves are afoot to replace the entire world supply" of artemisinin. "Early on, it was not about replacing the agricultural form … and now I think it's nearly inevitable that it will shift over" (Thomas 2013). Civil society organizations have long been concerned that this might be an impact of semi-synthetic artemisinin (Thomas 2013; FOE *et al.* 2012). 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, 36).

122. As noted in several comments on an earlier draft of this document, the displacement of crops of small-scale farmers is not an impact unique to synthetic biology, nor are the experiences of these farmers pre-determined. **Indeed, displacement of natural products by synthetic-biology produced versions follow a "tradition of major technological advances that have displaced former methods of production"** (Wellhausen and Mukunda 2009, 115). 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*, 117). Using the historical examples of natural rubber and indigo dyes' competition with synthetic (chemical) versions, 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.* 119). 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, 40). 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 2010; ETC 2007).

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[69] 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.

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

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

123. **Although artemisinin is the most 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).

124. **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 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, 119). The example of artemisinin is frequently put forth 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, 11). 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, 45). 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).

3.3 Human health considerations relating to biodiversity

125. **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.

126. Traditional 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 conventional genetic engineering are not always clear.**

127. **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, 100). 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 3.1, 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 bacteria to target, penetrate regress tumors (Forbes 2010; Khalil & Collins 2010; Wieland & Fussenegger 2012). In December 2013, two "synthetic biology" companies, 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.

128. **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 2.2), 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, 42). 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 3.5) (König *et al.* 2013).

3.4 Ethical considerations relating to biodiversity

129. **Ethical considerations of biodiversity and of how humans relate to biodiversity are recognized as important in the context of the CBD.** For example, CBD COP X 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)).

130. **Starting as early as 1999, ethicists have actively engaged with the new tools and techniques of modern 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.

131. **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.* 388). 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, 35). 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, 28). 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.

132. **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, 385). 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 genes' expressions. 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" (ECNH 2010, 11; Cho *et al.* 1999; Boldt and Müller 2008). 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).

133. **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, 588). 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).

134. **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, 71). 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.

135. **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 synthetic biology organisms, 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 natural DNA sequences (ie, "life") (Torrance 2010).

3.5 Intellectual property considerations related to biodiversity

136. **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).

137. **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 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 MIT-hosted Registry of Standard Biological Parts, contributing researchers post their BioBrick™ parts, DNA-sequences that incorporate standardized sections. The BioBricks Foundation has 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).

138. **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's possible that an additional challenge for conservation biologists and synthetic biologists to work together could be that the types of biological knowledges used by synthetic biologists are "much more restricted" (Redford *et al.* 2013).

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

Social, economic and cultural considerations	Possible positive and negative impacts of synthetic biology
Biosecurity	Synthetic biology techniques may provide tools for better detecting and identifying pathogenic agents, and responding to biosecurity threats, for example through accelerated vaccine production (Endy 2005; Mukunda *et al.* 2009; PCSBI 2010)
	Synthetic biology techniques may raise a "dual use" challenge, in that the substances used by research for positive ends may also be used for damaging results, such as creating destructive pathogens that target natural resources (Kaebnick 2009; Mukunda *et al.* 2009)
Economic	Synthetic biology is widely anticipated to play a significant role in the bioeconomy, which could benefit the economic growth (and human health and environment) of countries (EC 2012a; US White House 2012) Synthetic biology alternatives for natural products may lead to product displacement in developing countries, but potential harms may be addressed through product-specific arrangements and public engagement (Garfinkel & Friedman 2010; RAE 2009) or the natural version may still hold on to some share of the market, or the benefits of the synthetic biology versions may outweigh the losses (Wellhausen & Mukunda 2009) Potential harms from product-displacement may be addressed through product-specific arrangements and public engagement (Garfinkel & Friedman 2010; RAE 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)
	Synthetic biology may aid in diagnostics (PCSBI 2010)
	Synthetic biology may aid in drug discovery through developing drug screening platforms (Pauwels *et al.* 2012)
	Synthetic biology may help design organisms to produce drugs and vaccines (Dormitzer *et al.* 2013; Mueller *et al.* 2010; Ro *et al.* 2006)
	Synthetic biology may 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 labs (FOE *et al.* 2012; PCSBI 2010)
	Patent thickets and broad patents may restrict access to drugs and therapies (König *et al.* 2013)
Ethical	*Ethical discussions around synthetic biology are not structured around potential "positive" and "negative" impacts, but rather broad considerations:*
	Ethical analysis may help determine how to weigh and balance possible negative impacts of synthetic biology against possible positive impacts, as well as explore what equitable distribution of synthetic biology-related harms and benefits would look like and how to achieve this (Anderson *et al.* 2012; EGE 2009; Nuffield 2012; Parens *et al.* 2009)
	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) ...*counter* ... Ethical discussions should not be based on assumptions that synthetic biology is able to do more than it can (Marris & Rose 2012)
	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) ...*counter*... "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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