**A Submission to the Convention on Biological Diversity's**
**Subsidiary Body on Scientific, Technical and Technological Advice**
**(SBSTTA)**
**on the Potential Impacts of Synthetic Biology**
**on the Conservation and Sustainable Use of Biodiversity**

**Submitted by:**

**The International Civil Society Working Group on Synthetic Biology**

**Consisting of**

**Action Group On Erosion, Technology and Concentration (ETC Group)**
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**International Center for Technology Assessment**
**The Sustainability Council of New Zealand**

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# A Submission to the Convention on Biological Diversity's Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) on the Potential Impacts of Synthetic Biology on the Conservation and Sustainable Use of Biodiversity

## Contents

## Recommendations

## References

## Executive Summary

In accordance with CBD Decision X/13, paragraph 4, the following paper is submitted to the Subsidiary Body on Scientific, Technical and Technological Advice for its consideration. This submission examines the potential impacts of synthetic biology and its relevance to the three objectives of the Convention on Biological Diversity: the conservation and sustainable use of biodiversity and the fair and equitable sharing of benefits arising from the utilization of genetic resources.

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. While synthetic biology incorporates the techniques of molecular biology, it differs from recombinant DNA technology.

SBSTTA must not defer its consideration of synthetic biology as a new and emerging issue requiring governance. Synthetic biology is a field of rapidly growing industrial interest. A handful of products have reached the commercial market and others are in pre-commercial stages. OECD countries currently dominate synthetic biology R&D and deployment, but basic and applied research is taking place in at least 36 countries worldwide. Many of the world's largest energy, chemical, forestry, pharmaceutical, food and agribusiness corporations are investing in synthetic biology R&D. Current applications of synthetic biology focus on three major product areas that depend heavily on biomass feedstock production processes: 1) biofuels; 2) specialty and bulk chemicals; 3) natural product synthesis.

**The emerging issue of synthetic biology requires urgent attention by the SBSTTA because:**

- Applications of synthetic biology pose enormous potential impacts on biodiversity and the livelihood and food security of smallholder farmers, forest-dwellers, livestock-keepers and fishing communities who depend on biodiversity, especially in the developing world. With an estimated 86% of global biomass stored in the tropics or subtropics, developing countries are already being tapped as the major source of biomass to supply industrial-scale feedstock for synthetic biology's fermentation tanks and biorefineries. To date, no studies have systematically examined the increased demand for biomass, and the subsequent impact on biodiversity and land use, that may result from the provision of biomass feedstocks for industrial-scale fermentation by synthetic organisms.

- New, natural substitutes manufactured by organisms that are modified with synthetic DNA have the potential to adversely impact traditional commodity exports and displace the livelihoods of farmers and agricultural workers. Synthetic biology researchers are actively developing new, bio-based substitutes for plant-based tropical commodities such as vanillin, rubber (isoprene), stevia, pyrethrin,

artemisinin, liquorice, among others. No inter-governmental body is addressing the potential disruptive impacts of synthetic biology on developing economies, particularly poor countries that depend on agricultural export commodities.

- The behavior of synthetic biological systems is inherently uncertain and unpredictable, yet the precautionary principle is not guiding research and development of synthetic organisms. Risk assessment protocols have not yet been developed to assess the potential ecological risks associated with synthetic biology. Synthetic organisms are currently being developed for commercial uses in partial physical containment (i.e. fermentation tanks or bioreactors) as well as for intentional non-contained use in the environment. Many of the researchers who are most active in the field of synthetic biology do not have training in biological sciences, biosafety or ecology.

- Although existing national laws and regulations may apply to some aspects of the emerging field of synthetic biology, there is no comprehensive regulatory apparatus for synthetic biology at the national or international level.

- Rules and procedures for the safe transfer, handling and use of LMOs under the Cartagena Protocol on Biosafety and the Nagoya–Kuala Lumpur Supplementary Protocol to the Cartagena Protocol on Biosafety, do not sufficiently extend to synthetic organisms or genetic parts developed by synthetic biology . In addition, the evolution of synthetic biology, genomics and chemical synthesis of DNA could profoundly alter current practices related to the conservation and sustainable use of biodiversity and rules governing access and benefit sharing.

- The Biological Toxin and Weapons Convention addresses some biosecurity risks associated with synthetic biology, but no intergovernmental body is currently addressing the potential impacts of synthetic biology on land use, biodiversity and associated livelihoods. Similarly, potential biosafety impacts of synthetic biology on the conservation and sustainable use of biological diversity are not being addressed by any intergovernmental body.

**The new and emerging issue of synthetic biology is relevant to the attainment of the objectives of the CBD, its thematic programmes of work and cross-cutting issues.**

Current applications and potential impacts of synthetic biology touch on conservation and sustainable use of biodiversity at all levels: genes, species and ecosystems. Current R&D on synthetic biology extends to both marine and terrestrial organisms. As a result, the new and emerging issue of synthetic biology is relevant to virtually all of the CBD's thematic programmes of work, including: Agricultural Biodiversity; Dry and Sub-humid Land Biodiversity; Forest Biodiversity; Inland Waters Biodiversity; Island

Biodiversity; Marine and Coastal Biodiversity. Synthetic biology is also relevant to many cross-cutting issues, especially: Biodiversity for Development, Sustainable Use of Biodiversity, Traditional Knowledge, Innovations and Practices - Article 8(j); Climate Change and Biodiversity; Ecosystem Approach; Invasive Alien Species; and Technology Transfer and Cooperation.

**Recommendations**

**We recommend that SBSTTA, in the development of options and advice on the new and emerging issue of synthetic biology for the consideration of COP11, consider the following actions/recommendations:**

**Recommended Actions under the Convention on Biological Diversity**

- Parties to the Convention on Biological Diversity, in accordance with the precautionary principle, which is key when dealing with new and emerging scientific and technological issues, should ensure that synthetic genetic parts[1] and living modified organisms produced by synthetic biology are not released into the environment or approved for commercial use until there is an adequate scientific basis on which to justify such activities and due consideration is given to the associated risks for biological diversity, also including socio-economic risks and risks to the environment, human health, livelihoods, culture and traditional knowledge, practices and innovations.

- As first steps in addressing these tasks Parties should submit views and national experiences and identify gaps in the governance of synthetic genetic parts and living modified organisms produced by synthetic biology as developed for release or commercial use to the Executive Secretary. Parties should request the Executive Secretary to consolidate the submissions as a basis for further work and convene an Ad-hoc Technical Expert Group which is regionally balanced and comprises all the necessary fields and backgrounds to make a comprehensive assessment, i.e. including molecular biology, ecology, environmental sciences, socio-economic and legal expertise, and also including indigenous peoples, local communities, civil society representatives, farmers, pastoralists, fisherfolk and other stakeholders with the mandate to:

i) Analyse the adequacy of existing assessment frameworks and identify gaps in knowledge and methodologies for assessing the potential negative

1 Further analysis is required to determine which synthetic genetic parts should be covered under this proposal.

impacts of synthetic genetic parts and living modified organisms produced by synthetic biology on biodiversity and the environment.

ii) Assess the impact on traditional knowledge, practices and innovations, customary law, human rights and livelihoods, including customary use of biological diversity by indigenous peoples and local communities, farmers, pastoralists and fisherfolk that may ensue from the appropriation of land, sea and biomass and replacement of natural compounds by industrial production systems that utilize synthetic genetic parts and living modified organisms produced by synthetic biology.

- Acknowledging the model character of Article 14 of the Cartagena Protocol on Biosafety which deals with Impact Assessment and Minimizing Adverse Impacts of products of modern biotechnology, Parties should adopt legal, administrative and policy measures regarding environmental impact assessment of proposed synthetic biology projects that may have significant adverse effects on biological diversity. This should include synthetic genetic parts and living modified organisms produced by synthetic biology intended for release into the environment as well as those destined for contained use, due to the fact that effective containment in the context of synthetic biology may require updating and upgrading of the containment facilities.

- In line with decision V.5 III, The Conference of the Parties should recommend that, in the current absence of reliable data on biocontainment strategies based upon synthetic biology, including xenobiology, mirror biology, alternative nucleotides or other synthetic biology approaches, without which there is an inadequate basis on which to assess their potential risks, and in accordance with the precautionary principle, products incorporating such technologies should not be approved by Parties 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. In order to enhance the capacity of all countries to address these issues, Parties should widely disseminate information on scientific assessments, including through the clearing-house mechanism, and share their expertise in this regard;

- The Conference of the Parties should initiate the development of a mechanism, treaty or protocol to enable more rapid assessment of emerging technologies such as synthetic biology where they are relevant to the conservation and sustainable use of biological diversity and fair and equitable sharing of genetic resources. Such a mechanism, treaty or protocol, based on the precautionary principle, should provide for the anticipatory evaluation of societal, economic,

cultural as well as environmental and health impacts of emerging technologies and sharing of information between parties and other stakeholders

**Recommended Actions under the Cartagena Protocol on Biosafety and the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress**

- Acknowledging the importance of complying with the objectives and articles of the Convention when faced with rapid scientific and technological innovations, the Conference of the Parties should invite the Parties to the Cartagena Protocol on Biosafety and the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to:

i) Consider extending requirements for advance informed agreement and risk assessment procedures to synthetic genetic parts in order to cover gaps that otherwise permit evasion of the rules agreed under the protocols. One gap arises from new techniques that make it possible to import DNA sequences over the internet, such that no physical transfer takes place. A second gap arises from related techniques that allow an LMO to be imported as a set of parts ready to be reconstituted, rather than a whole viable organism. These threats to the objectives of the protocol could be addressed by extending advance informed agreement rules so that they also apply to:

- - Agents that construct an LMO, whether from electronic code or genetic parts; and
- - Agents that export genetic parts (such as biobricks) that are "latently viable" (parts deemed to posses sufficient latent potential to form or promote the formation of a viable organism).

ii) Consider excluding from the ‘contained use’ provisions, synthetic genetic parts and living modified organisms produced by synthetic biology, in order to address the new containment challenges they pose - at least until effective containment methods can be demonstrated. Thus the Article 6.2 exemption from having to obtain advance informed agreement for contained use would not apply.

[iii) Consider the case in which an agent imports an LMO into containment (without obtaining advance informed agreement) and subsequently seeks to take it outside containment, that such an agent be then required to obtain an approval from the domestic regulator based on a risk assessment process that is at least as strong as set out in Annex III of the protocol. This is to avoid an agent being able to gain advantage in jurisdictions where the domestic requirements are weaker than apply under Annex III.

**Reccomended Actions under the Nagoya Protocol on Access and Benefit Sharing**

- The Conference of the Parties should further invite the parties to the Nagoya Protocol on Access and Benefit Sharing to consider extending agreements on access and benefit sharing to cover digital genetic sequences and products derived from natural sequences using synthetic biology tools such as directed evolution techniques.

**Part 1: Introduction and Overview: What is 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 characterised and whose behavior can be rationally predicted.

Synthetic biology is not a discrete technology or scientific discipline; it is best understood in the context of multiple and converging scientific and technological disciplines. In particular, synthetic biology involves molecular biology, genomics, engineering, nanobiotechnology and information technology.

Although there is no universally accepted definition, synthetic biology has been defined by a number of scientific and/or governmental bodies. For example:

*"Synthetic biology is an emerging area of research that can broadly be described as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems."* - U.K. Royal Society[2]

*Synthetic biology is the engineering of biological components and systems that do not exist in nature and the re-engineering of existing biological elements; it is determined on the intentional design of artificial biological systems rather than on the understanding of natural biology.* European Commission Directorate-General on Research (October 2005)

The foundational technologies underlying synthetic biology are the extraordinarily rapid advances in the efficiency of DNA sequencing, synthesis and amplification over the past 20 years. DNA synthesis technologies are becoming cheaper, faster and widely accessible. Using a computer, published gene sequence information and mail-order synthetic DNA from commercial DNA "foundries," researchers are constructing genes or entire genomes from scratch – including those of dangerous pathogens. Other researchers are experimenting with entirely new types of DNA composed of nucleotide bases and amino acids that are not found in nature. Yet others are synthetically constructing non-nucleotide parts of cellular systems: i.e., cells, RNA, ribosomes, membranes etc.

The conceptual basis underlying current approaches to synthetic biology is a reductionist, mechanistic view which accepts that the phenotypic effects of genes are the straightforward result of chemical and physical processes (European Commission 2009). Simply put, a reductionist view of synthetic biology assumes that the behaviour and function of intentionally designed, synthetic organisms will be controlled by synthesised DNA sequences.

2 http://royalsociety.org

Although the reductionist view has dominated biology for several decades, it stands in contrast to newer concepts in the field of gene-ecology and *epigenetics*[3] which call for more complex concepts of the gene, based not only on its DNA sequence, but also evolutionary pressures that create a growing complexity of interaction at all levels (Presidential Commission 2010). Borrowing concepts from engineering and computing, some synthetic biologists believe that it will be possible to develop biological parts that are "evolutionarily selected for not depending on the biological context of the recipient" (Lorenzo and Danchin 2008). In the lexicon of synthetic biologists, the so-called context-independent biological function is called "orthogonality."

**Synthetic biology is not synonymous with recombinant DNA technology:** While synthetic biology incorporates the techniques of molecular biology, it differs from recombinant DNA technology. Transgenic organisms result from the introduction of naturally occurring, mutated or otherwise altered DNA into an organism with the source of DNA being an organism of a different or the same species. By contrast, synthetic biology introduces synthetically constructed parts and is not limited to the modification of natural organisms, but also extends to the construction of new life forms with no natural counterpart. Synthetic biology is also considered distinct from recombinant DNA because of the *complexity* of engineered organisms or systems that researchers seek to create and/or manipulate. Rather than focus on expression of single genes or gene components, the work of synthetic biologists may involve whole interacting genetic networks, genomes and entire organisms (European Commission 2009, p. 15). Rather than modifying existing biological systems, synthetic biologists are designing and fabricating new ones that are built with DNA that is partially or entirely artificial.

**Distinct approaches that fall under the umbrella of synthetic biology include:**

***"Biobricks" construction***

Early work in synthetic biology, inspired by microelectronic engineering, has focused on the development of simple "gene circuits" that seek to control cell biochemistry in pre-determined ways. The term "biobricks" refers to prefabricated, standardized and modular DNA sequences that code for certain functions. The development of standardized biological parts is popularly known as the "lego-ization of biology." The expectation is that standard biological parts can be freely combined and incorporated into living cells to construct new biological systems and devices that will work as "programmed". Although the online, open access "registry of standard biological parts" includes over ten thousand entries, some observers note

3 Epigenetics refers to the study of heritable changes in gene expression that are not due to changes in DNA sequence.

that the vast majority of these parts have not been thoroughly characterized and do not work as designed (Schmidt and Pei 2010; Kean 2011).[4]

***Metabolic pathway engineering***

Metabolic engineering refers to the altering of several interacting genes or the introduction of newmetabolic pathways within a cell or microorganism to direct the production of a specific substance, including the synthesis of natural products (pharmaceutical ingredients, flavours, fragrances, oils, etc.) as well as high-value chemicals, plastics and fuels. These compounds may not normally be produced in the engineered cell. Typically in synthetic biology metabolic pathways are engineered into microbes which use plant-derived sugars (biomass) as a power source to biologically synthesise a desired chemical. In this way researchers have achieved microbial production of natural products by transferring or constructing de novo product-specific enzymes or entire metabolic pathways from a rare or genetically intractable organism to a microbial host that can be engineered to produce the desired product (Keasling 2010). For example, researchers have successfully engineered the metabolic pathway of a yeast with 12 new synthetic genetic parts so that the yeast produces artemisinic acid, a precursor of antimalarial compound artemisinin typically sourced from the Chinese sweet wormwood plant (Withers and Keasling 2007). Metabolic engineering of plants, insects and mammals is also being developed. Advances in metabolic pathway and protein engineering have also made it possible to engineer microorganisms that produce hydrocarbons with properties that are similar or identical to petroleum-derived transportation fuels (Keasling 2010), or to microbially produce chemicals that are currently derived from non-renewable petroleum – moving production from chemical manufacturing facilities to living cells. In the words of one synthetic biologist, “metabolic engineering will soon rival and potentially eclipse synthetic organic chemistry” (Keasling 2010, p. 1355).

***Whole genome engineering and construction***

Synthetic Genomics refers to efforts to construct any specified gene or full genome for which the complete DNA sequence is known by assembling synthetic (chemically produced) DNA strands (oligonucleotides). This may include novel sequences. Researchers have used existing genomic sequence information to construct whole-length genomes from scratch. In 2002 researchers synthesised the 7,741 base poliovirus genome from its published sequence, producing the first synthetic virus constructed from DNA sequences. In 2005 scientists synthesised the virus responsible for the 1918-19 flu pandemic. In 2008, scientists at the J. Craig Venter Institute performed the first-ever complete *de novo* synthesis of a whole bacterial genome (the 582,970 base pair *M. genitalium* bacterial genome) (Gibson et al. 2008). In May 2010 the Venter Institute announced the landmark technical feat of constructing a 1 million-base-pair genome – the world’s first organism with a completely synthetic genome – and its insertion in a functional (non-synthetic) bacterial cell (Gibson et al. 2010). Dr. Venter described the

4 At a meeting of synthetic biologists in July 2010 participants noted that, of the 13,413 parts listed then in MIT’s Registry of Standard Biological Parts, 11,084 did not work. See, S. Kean, “A lab of their own,” *Science*, Vol 333, 2 Sept. 2011, p. 1241.

converted cell as “the first self-replicating species we’ve had on the planet whose parent is a computer” (Wade 2010). The practical application of the quest to develop a “minimal genome” – in which an existing genome is pared down to the minimum number of genes needed to ensure the organisms’ survival – is to develop a synthetic “chassis” to which designed synthetic DNA sequences can be more easily added to confer new, pre-determined functions.

### *“Directed evolution” approaches*

**‘**Directed Evolution’ describes techniques that attempt to rapidly ‘evolve’ novel DNA sequences or expressed proteins either in the lab or in a computer towards a particular outcome. Typically, directed evolution techniques involve selecting an existing genetic sequence and creating an array of mutations which are then introduced into a model organism and screened for a specific outcome (e.g. production of a chemical or improved photosynthesis). Mutation may be created in vivo or in silico. Bioinformatic tools are used to predict the fitness of sequences, which can then be synthesised. In another example, genetic sequences inserted into a synthetic chromosome can be triggered by a chemical, resulting in the rearrangement of the organisms’ genes. The technique, known as “genome scrambling,” enables scientists to experiment with thousands of new strains, hand pick the survivors and thereby accelerate the evolution of the synthetic organisms by design. In September 2011 scientists announced that they have used this technique to develop synthetically produced DNA that replaced all of the DNA in the arm of a chromosome of the yeast, *Saccharomyces cerevisiae* (Dymond et al. 2011). While the synthetic DNA is structurally distinct from the replaced part of the yeast’s natural chromosome, the resulting cell is indistinguishable in its growth properties from the native yeast (Dymond et al. 2011). Other ‘in vivo’ synthetic biology approaches include the ‘combinatorial genomics’[5] approach developed by scientists of the J. Craig Venter Institute and Multiplex-automated genomic engineering (or MAGE) developed at Harvard University both of which apply robotic genome assembly methods to fabricate thousands of variants of viable synthetic organisms in parallel for screening for specific traits and fitness – emulating the approach of combinatorial chemistry for drug development (Singer 2009).

### *Engineering microbial consortia*

The term “metagenomics” refers to genome sequencing projects in which many organisms are sequenced at once. (Binnewies et al. 2006). Some synthetic biologists are attempting to design ‘consortia’ of microbes that collaborate towards a specific outcome such as digesting biomass into sugars or fermenting sugars into fuels. Microbial consortia are ‘engineered’ in the sense that they may bring together microbes that might not have coexisted previously, and may also involve synthetic microbes that are

5 For more information on combinatorial genomics, see: European Patent Application EP2255013, “Methods for in vitro joining and combinatorial assembly of nucleic acid molecules.”

engineered to work together for an industrial purpose. In the words of one synthetic biologist, “Given that microbial consortia can perform even more complicated tasks and endure more changeable environments than monocultures can, they represent an important new frontier for synthetic biology” (Brenner et al. 2008).

***Alternative genetic systems and other synthetic cellular elements***

While much of synthetic biology focuses on the ‘re-writing’ of DNA codes, some researchers are focusing on the development of alternative genetic systems, including synthetic nucleic acids, amino acids, and other cellular elements. In 2011, for example, chemists announced that they had produced artificial nucleotide bases capable of evolving to produce new genes (Yang et al. 2011). This artificial genetic code consists of six bases, rather than the standard four. The synthetic DNA molecules, dubbed ‘P’ and ‘Z’ can be inserted into DNA alongside the standard four bases: adenine – (A), thymine (T), cytosine (C) and guanine (G). The researchers report that the six artificial DNA bases have replicated in artificial cells, and intend as a next step to introduce the bases into *E. coli*. University of Florida chemist, Steve Benner, has developed two additional functional bases (‘k’ and ‘x’) and a nucleic acid encoding system known as AEGIS (An Expanded Genetic information System), with up to 12 different bases arranged in 6 pairs. AEGIS is used commercially for diagnostic medical tests (Yang et al. 2006).

Other synthetic biologists have developed nucleic acids that structurally diverge from DNA. In 2003, Eric Kool of Stanford University published work on the construction of a larger DNA molecule known as xDNA (for expanded DNA) which does not interact with standard DNA (Liu et al. 2003). Scientists at Los Alamos National Laboratory in the U.S. are developing a peptide based nucleic acid (called PNA) which connects the existing chemical bases of DNA with a peptide backbone instead of a sugar phosphate backbone (Petersson et al. 2001).

Synthetic biologists at Harvard University and the Massachusetts Institute of Technology are developing alternative genetic systems known as “mirror biology” (Bohannon 2010). So-called “mirror life” is based on DNA and proteins that are mirror images of each other, a property called chirality. In theory, a cell could be based on the workings of “wrong-handed” amino acids. Researchers are attempting to build a synthetic ribosome capable of stringing together wrong-handed amino acids, and then translating them into mirror proteins. Mirror life systems would mimic the biochemistry of existing life but theoretically be incompatible with earthly life, suggesting that built-from-scratch mirror molecules would come with built-in biosafety features (see discussion of xenobiology below). However, even the scientists most intimately involved in the creation of mirror life point out that there are potentially grave safety issues associated with mirror biology, including unexpected side effects as shown by the case of the anti-nausea drug thalidomide, where chirality was unexpectedly linked to birth defects.

Other synthetic biologists have incorporated non-natural amino acids (beyond the standard 20 amino acids) into protein molecules (Voloshchuk and Montclare 2010). Scientists have successfully modified bacterial, yeast

and mammalian cells to code for non-natural amino acids (Schmidt 2010). Beyond exploring the structure and functioning of protein molecules, researchers seek to one day incorporate artificial genes into microbes that encode non-natural proteins with novel and potentially useful properties.

***Building Protocells and cell-free systems***

Researchers are testing combinations of non-living chemical components in an attempt to create protocells, or synthetic life without DNA (Sole et al. 2007). The aim is to create artificial cell-like devices (vesicles) with simplified genetic machinery that can replicate and pass on genetic information. In theory, artificial systems that synthesise biological molecules would be less complex and therefore easier to control, adapt and sustain than natural cells (IRGC 2010). Others are developing non-biological vesicles such as microfluidic chips which build and then express strands of synthetic DNA in silicon chambers to produce compounds of interest (Kong et al. 2007).

## Current and Near-Term Applications of Synthetic Biology

The United States and Europe currently dominate R&D in the field of synthetic biology, but basic and applied research is taking place in at least 36 countries worldwide (Oldham and Hall 2011). From 2005-2010, governments in the United States and Europe allocated more than US$500 million toward synthetic biology research in more than 200 locations (Woodrow Wilson International Center 2010). Synthetic biology is a field of rapidly growing industrial interest. Dozens of start-up companies that self-identify as synthetic biology firms have entered high-profile partnerships with transnational energy, chemical, forestry, pharmaceutical, food and agribusiness corporations to bring products to market. For example, six of the world's top 10 energy corporations have entered R&D partnerships or business agreements with synthetic biology start-ups; six of the world's top 10 grain traders and six of the world's top 10 chemical corporations have also invested or struck partnerships in synthetic biology R&D. (See tables below.) A handful of products engineered with synthetic biology have already reached commercial markets, and are produced in vats of synthetic organisms in commercial settings; many more are in pre-market stages.

**Synthetic organisms are currently being developed for commercial uses in settings with only partial physical containment (i.e. fermentation tanks or bioreactors) as well as for intentional non-contained use in the environment (i.e. biofuel production with synthetically modified algae in open-air ponds).**

Because it is not a discrete industry sector, efforts to measure the economic impacts of synthetic biology are imprecise. One industry analyst values the synthetic biology market at $233.8 million in 2008 and predicts an almost 60 percent annual growth rate to $2.4 billion in 2013 (BCC Research 2009). Another estimate expects the market to reach $4.5 billion by 2015, noting that what began as a North American and European industry is gaining traction in Japan, China and other Asian economies (Global Industry Analysts

2010). According to Lux Research Synthetic biology startups in the biofuels and bio-based chemicals sector have already received $1.84 billion in private funds since 2004 which amounts to fully 28.4% of all biofuel investment during that period. The rate of investment has shot up in recent years with a 25% increase in investments recorded between 2009 and 2010.[6]

**Top Ten Energy Corporations:**
**Partnerships with Synthetic Biology Companies**

| Energy Corporation | Synthetic Biology Partner(s) |
|---|---|
| 1. Royal Dutch Shell | Amyris, Codexis, Iogen, (LS9) |
| 2. Exxon Mobil | Synthetic Genomics |
| 3. British Petroleum | Synthetic Genomics, Verenium, DuPont, Amyris, Qteros, Verdezyne |
| 4. China Petroleum | |
| 5. Chevron Corporation | Solazyme, LS9, Catchlight |
| 6. Total SA | Amyris, Gevo |
| 7. Petrochina | |
| 8. E.On AG | |
| 9. Petrobras | KL Energy, Amyris, Novozymes |
| 10. Gazprom | |

**Top Ten Chemical Corporations:**
**Partnerships with Synthetic Biology Companies**

| Chemical Corporation | Synthetic Biology Partner(s) |
|---|---|
| 1.BASF (Germany) | Evolva, Verenium |
| 2.Dow (USA) | Solazyme, Algenol |
| 3.Sinopec | |
| 4.Ineos Group | |
| 5.Exxon Mobil (USA) | Synthetic Genomics |
| 6.DuPont (USA) | BioArchitecture Lab, Butamax |
| 7.Formosa Plastics | |
| 8.Royal Dutch Shell (UK) | Amyris, Codexis, Iogen |
| 9. SABIC | |
| 10. Total | Amyris, Gevo |

**Top Ten Grain Traders:**
**Partnerships with Synthetic Biology Companies**

| Grain Trader | Synthetic Biology Partner(s) |
|---|---|
| 1. Cargill | Virent, Zeachem, Verenium, Gevo |
| 2. Archers Daniel Midland | Metabolix |
| 3. Bunge | Verenium, Solazyme , Amyris |
| 4. Marubeni | |
| 5. Itochu | |
| 6. Louis Dreyfus/Santelisa Vale | Amyris |
| 7. Noble Group | |
| 8. China National Cereals, Oils and Foodstuffs | |
| 9. Wilmar International | Amyris |
| 10. Associated British | DuPont Biofuels |

6 Christie Oliver, “Investors Pump $930 Million into Alternative Fuel Technologies”, Lux Populi Newsletter -- September 18, 2011

**Current applications of synthetic biology focus on four major product areas – three of which depend heavily on biomass feedstock production processes:** 1) biofuels; 2) specialty and bulk chemicals; 3) natural product synthesis, including medical compounds; 4)biomedical applications. Examples of each major area are provided below.

**1) The development of synthetic microbes and enzymes to break down biomass into biofuels, and the engineering of algae to yield higher concentrations of oil/fuels:**

- Companies such as Amyris Biotechnologies, LS9, Solazyme and Synthetic Genomics, Inc. are working with corporate partners to develop microbes and microalgae to ferment sugar or cellulose into next generation biofuels, or to directly produce oils, respectively. The goal is to engineer synthetic microbes and/or microalgae to efficiently break down cellulose and convert carbohydrate sugars to hydrocarbon fuels that are more energy-rich than ethanol, or to engineer algae to produce oils at concentrations higher than those found naturally, or to yield algal oils that closely resemble fuels such as petroleum or aviation fuel.

- Solazyme claims that its engineered algal strains, grown in bioreactors and fed sugars, have an oil content exceeding 80% of their weight. In 2010, Solazyme produced over 80,000 liters of algal-derived marine diesel and jet fuel under contract to the U.S. Navy.[7] Solazyme is also selling 20 million gallons of algal-derived oil to Dow for use as insulating fluid for electric transformers.

- U.S.-based synthetic biology company Bio Architecture Lab (BAL) claims to have developed a novel biosynthetic pathway that converts aquafarmed macroalgae (seaweed) into biofuels. BAL is collaborating with Chilean oil company, ENAP, to develop Chilean seaweed farms for ethanol and partnering with Norwegian oil giant Statoil to develop a second seaweed-to-ethanol farm in Norway (Lane 2010a). BAL also partners with chemical giant DuPont to turn seaweed to isobutanol (a more energy-rich fuel than ethanol) using synthetic microbes (Lane 2010b).

- Mascoma, with investments from General Motors, Marathon Oil and Valero is preparing to open a commercial scale wood-based cellulosic ethanol biorefinery that uses synthetic microbes to turn woodchips from North American forests into cellulosic ethanol in a ‘one pot’ process.[8] The company is collaborating with Stellenbosch Biomass

7 http://www.solazyme.com/fuels

8 http://www.mascoma.com/

Technologies to introduce the same technology to South Africa (Lane 2010c).

- Sapphire Energy, who are developing algal strains through synthetic biology, is building a 300-acre open pond algae farm in New Mexico for pre-commercial demonstration to produce algae-based biofuel.[9] The company has received $104.5 million in U.S. government funding for the project.

**2) Synthetic microbes engineered to produce unnatural specialty and bulk chemicals (i.e., plastics)**

- Agrochemical firm, DuPont in a joint venture with sugar giant Tate and Lyle, already uses synthetically altered yeast to ferment corn sugars that produce propanediol, an essential building block used to manufacture the company's synthetic thermoplastic polymer fibre, marketed as Sorona. Dupont says its bio-fibre will eventually replace nylon, and is already being used in the manufacture of apparel, carpeting and more.

- Adipic acid is a chemical used to make Spandex and other polymers with an annual market value of over US$5 billion. Adipic acid is typically manufactured via synthetic organic chemistry. Verdezyne, Inc. – a privately-held synthetic biology company with undisclosed investments from British oil giant BP and Dutch biochemicals company DSM– is engineering the metabolic pathway of yeast to produce adipic acid via a bio-based fermentation process.[10] Using sugar or plant-derived oils as a feedstock, the company estimates that it can cut the cost of manufacturing adipic acid by at least 20%.[11]

**3) Synthetic microbes for the production of natural product synthesis:**

- In nature, the malarial drug artemisinin is produced by the Chinese sweet wormwood plant, *Artemisia annua*. In pursuit of a cheaper and more reliable source of artemisinin, which is now sourced globally from farmers in Africa and Asia, researchers at the California-based Amyris, Inc., successfully engineered the metabolic pathway of a yeast to produce artemisinic acid, a precursor of artemisinin (Withers and Keasling 2007). The engineering involved in constructing an artificial pathway in yeast to produce artemesinic acid is exceedingly complex, involving ten genes from four organisms. Amyris has licensed its technology to pharmaceutical firm Sanofi-aventis for the scale-up and possible commercialization at a facility in eastern europe, which could

9 http://www.sapphireenergy.com

10 http://www.verdezyne.com

11 http://www.verdezyne.com

reach the market by 2013.[12] See case study below.

- Genencor (owned by DuPont) has used synthetic biology to engineer the metabolic pathway of *Escherichia coli* to express the gene encoding isoprene, an important commodity chemical used in many industrial applications, including the production of synthetic rubber. Genencor and Goodyear Tire and Rubber are developing BioIsoprene for commercial production and have already produced prototype tyres made with BioIsoprene. See case study below.

**4) Biomedical applications of synthetic biology:**

- In October 2010 Craig Venter announced the creation of a new company, Synthetic Genomics Vaccines, Inc., which has a three-year agreement with pharmaceutical company Novartis to create a bank of synthetic viruses for vaccine development (J. Craig Venter Institute 2010). According to Craig Venter's 2010 testimony to the U.S. Presidential Commission for the Study of Bioethical issues, with "rapid [DNA] sequencing and all these changes in reading the genetic code, and now the ability to quickly write the genetic code, it's now hours instead of weeks and months to make new [virus] seed stocks … It's very likely… the vaccine you get next year will be from synthetic genomic technologies." (Presidential Study for the Study of Bioethical Issues 2010). Synthetic biology is also being used to develop engineered viruses to invade and destroy cancer cells. According to a review of the biomedical applications of synthetic biology in *Science,* "In one study, the invasion was designed to occur only in specific tumor-related environments, whereas in another, the bacterial invaders were engineered to knock down a specific, endogenous cancer-related gene network (Ruder et al. 2011).
- Research is underway on techniques to reengineer the human microbiome – the complex ecosystem of over 1000 species of microorganisms associated with the human body and physiology, which outnumber human cells by a factor of 10 to 100 (Turnbaugh et al. 2007). For example, researchers recently engineered a synthetic interaction between E. coli and gut microbes intended to prevent cholera infection (Duan and March 2010).

## Part 2: Synthetic Biology, Biosafety and Biodiversity

**The behavior of synthetic biological systems is inherently uncertain and unpredictable and may be based on wrong and misleading metaphors.** Synthetic biology design tools are in their infancy and the behavior of synthetic biological systems is unpredictable (Keasling 2010; Kwok 2010; Presidential Commission for the Study of Bioethical Issues 2010). In part this unpredictability results from fundamental uncertainties about the behavior of genetic systems which make an engineering approach unstable.

12 http://www.amyris.com/markets/artemisinin

Synthetic biology as a field is infused with metaphors borrowed from computing and engineering sciences (i.e., ‘programming code,’ using a ‘chassis,’ ‘refactoring,’ gene ‘circuits,’ etc.) These mechanistic and computing metaphors may in fact poorly match the reality of biological systems (Keller 2004). While synthetic biologists attempt to characterize their genetic parts as a stable, predictable substrate for linear engineering approaches, in fact, the basic functioning of cellular and genetic systems may not suit the engineering approach. In particular insights from the study of epigenetics and more broadly from the fields of Developmental System Theory and Evolutionary Developmental Biology (Newman 2002).have qualified the role of the DNA code in organismal development and question whether it is even appropriate for synthetic biologists to talk of “programming” microbes.

The function of a cell “cannot typically be predicted based on its DNA sequence alone or by the shape and other characteristics of the proteins and the biological systems for which it codes (National Research Council 2010, p. 50). New research points to the importance of a chromosome’s shape and positioning inside a cell’s nucleus: the genomes of unicellular organisms form complex three-dimensional structures that are believed to have a significant role in genomic function (O’Sullivan 2011). The significance of spatial organization (shape and positioning) is not limited to the three-dimensional folding of the chromosome(s) in genomes, but also the folding and positioning of any additional genetic material present within complex genomes (O’Sullivan 2011).

Advances in epigenetics – the study of heritable changes in gene expression that are not due to changes in DNA sequence – also reveal previously unknown complexities in biological systems. For example, research in plants has found that environmental stressors (in this instance, the exposure of *Arabidopsis thaliana* to radiation) led to genomic changes not only in the exposed plant but also its progeny generations later (Molinier 2006).

These findings have important implications for the practice of inserting synthetic DNA sequences into a microbe such as an E. coli or yeast cell. They suggest that it may be extremely difficult to predict how the insertion of synthesised DNA into an organism will affect the organism’s function and its ability to survive in the wild. New human-made organisms with uncertain or unpredictable functions, interactions and properties could have adverse affects on the environment and biodiversity, and potentially pathogenic properties.

Structure-function predictions are a major challenge in biology, even in cases of non-engineered organisms. For example, the simplest predictions are thought to be for the relation of a DNA sequence and that of a protein, but experience shows that these supposedly simple predictions can be surprisingly difficult. Yoshida et al. found that three amino acid changes can transform the E. coli major folding chaperone, GroEL, into an insect toxin (Yoshida et al. 2001). When synthetic biologists endeavor to edit or alter the DNA code, other cellular components and activities, including DNA modifying

enzymes (which can effect gene expression levels), effects of the gene changes on translation rates (which can determine the folded shape of the protein product), and numerous other uncontrolled processes, they render the "engineered" result unpredictable.

Although computational models may help researchers predict cell behaviour, the cell is a complex and evolving system that is far different from standardized electronic parts. When synthetic gene circuits are placed into cells, for example, they can have unintended effects on their host (Kwok 2010). A research team at Duke University found that even a simple synthetic gene circuit can trigger complex and unintended behavior in host cells (Tan et al. 2009). When researchers activated a synthetic gene circuit in *E. coli*, they found that it retarded the cells' growth and subsequently slowed dilution of the gene's protein product; the circuit ultimately caused bistable gene expression (i.e., some cells expressed the gene, and others did not) (Tan et al. 2009).

**No risk assessment protocols have been developed to assess potential risks associated with synthetic biology – either for accidental releases of synthetic organisms from a lab or container, or risks associated with intentional non-contained use.**[13] Risk assessment is the methodology used to assemble and synthesise scientific information to determine whether a potential hazard exists and/or the extent of possible risk to human health, safety or the environment. Risk assessment has been an important tool in helping authorities make informed decisions regarding potential risk from living modified organisms (LMOs). Since the late 1980s, "substantial equivalence" has been the operative principle governing the regulation of transgenic crops in the United States – a doctrine that is not universally accepted and remains in dispute (Newman 2009; Millstone 1999). According to the doctrine of substantial equivalence, the potential risks of a transgenic plant can be compared and evaluated based on its naturally-occurring counterpart, as well as information about how the inserted genetic material would function within an engineered organism. Similarly, Annex 3 of the Cartagena Protocol provides that risks associated with living modified organisms (LMOs) or products thereof "should be considered in the context of the risks posed by the non-modified recipients or parental organisms in the likely potential receiving environment."[14]

For *de novo* organisms designed and constructed in the laboratory with chemically synthesised DNA – or for sequences containing both synthetic and natural DNA – there is no "parental organism" to be compared or evaluated.

13 A June 2010 survey of synthetic biology funding by governments in the United States and Europe conducted by the Woodrow Wilson International Center for Scholars searched "all relevant databases" but was unable to identify any public funding in the United States or Europe devoted to any type of risk assessment research on synthetic organisms. Source: Woodrow Wilson International Center for Scholars, Synthetic Biology Project. (2010). Trends In Synthetic Biology Research Funding In The United States And Europe. http://www.synbioproject.org

14 Cartagena Protocol on Biosafety, Annex 3, para. 5.

Synthetic biology researchers are currently experimenting with biological parts, devices and systems that have no analog in the natural world and no evolutionary or ecological history outside of the laboratory (Norton 2010).

The design and complexity of synthetic organisms presents additional challenges and uncertainty for standard risk assessment. Recent reports on synthetic biology acknowledge some of the potential risks:

*"… an organism assembled from genetic parts derived from synthetic or natural sources could display 'emergent behavior' not seen in the original sources…Existing risk assessment may not prove adequate for predicting outcomes in complex adaptive systems. In addition, while many scientists believe that engineered organisms are unlikely to survive or reproduce in a natural environment, the capability of synthetic organisms to mutate and evolve raises questions about the potential of synthetic organisms to spread and to exchange genetic materials with other organisms if released into the environment"* (Rodemeyer 2009).

*"Unmanaged release could, in theory, lead to undesired cross-breeding with other organisms, uncontrolled proliferation, crowding out of existing species and threats to biodiversity"* (U.S. Presidential Commission for the Study of Bioethical Issues 2010, p. 62).

*"One hypothetical, worst-case scenario is a newly engineered type of high-yielding blue-green algae cultivated for biofuel production unintentionally leaking from outdoor ponds and out-competing native algal growth. A durable synthetic biology-derived organism might then spread to natural waterways, where it might thrive, displace other species, and rob the ecosystem of vital nutrients, with negative consequences for the environment"* (U.S. Presidential Commission for the Study of Bioethical Issues 2010, p. 63).

In accordance with the Cartagena Protocol's general principles, "risk assessment should be carried out on a case-by-case basis."[15] Given the current state of knowledge, however, some scientists question whether regulatory agencies have the capacity to evaluate or monitor all new types of synthetic or partially synthetic organisms that are proposed for release. "Before regulatory agencies decide on whether an application for environmental release is acceptable, we need analyses of ecological risks and benefits. These analyses should not come just from industry. Ideally, results from independent research would be published in peer-reviewed journals and made available to the public…" (Snow 2011, p. 4). However, peer-reviewed studies on the ecological risks and benefits of synthetic organisms are not yet publicly available or have not been conducted.

Risk analysis of novel synthetic organisms will become more challenging as synthetic biologists gain the capacity to produce thousands of novel organisms at one time. As described above, synthetic biologist George

15 Cartagena Protocol on Biosafety, Annex 3, para. 6.

Church has invented multiplex automated genome engineering (MAGE) which was able to produce "over *4.3 billion combinatorial genomic variants per day*" (Wang 2009) [emphasis added]. It would be impossible to assess the risk of each novel organism when billions of organisms are created at once yet accidental release of large numbers of these variants must be considered likely at some point. Proper risk assessment methodologies must be created to determine how risk is measured in such circumstances, which types of genomic variations in which organisms will pose the most risk, and appropriate ways to mitigate those risks.

In July 2011 synthetic biology researchers came together for a day-long workshop in Washington D.C. to generate a preliminary framework for the comprehensive risk assessment of synthetic biology applications (Woodrow Wilson International Center 2011). The workshop used a hypothetical scenario involving the unintentional escape of cyanobacteria engineered to produce sugars to frame the discussion. In order to discuss risk assessment and synthetic organisms, the workshop participants made the following assumption: "Physical containment is not practical at a large scale production system. We should assume the GMO will enter local environment and disperse widely." (Woodrow Wilson International Center 2011). While the workshop provided a starting point to identify key questions on the fate and transport of synthetic DNA, the survival and persistence of the organisms, and the differences and functionality between the wild and novel organisms, the exercise was far from a complete risk analysis.

To date no risk assessment models have been developed or fully utilized for synthetic organisms – either at the research, product development or commercialization stage.

**Assured containment of organisms developed with synthetic biology is neither practical nor possible.** As noted above, there is a general assumption, even among experts in the field, that physical containment of synthetic organisms is not practical, especially within large scale production systems (Woodrow Wilson International Center 2011). A U.S. government presidential advisory board acknowledges that "contamination by accidental or intentional release of organisms developed with synthetic biology is among the principal anticipated risks" (Presidential Commission for the Study of Bioethical Issues 2010, p. 62).

Recent history indicates that accidents and other unanticipated events can lead to unintentional release of biological organisms, including those in laboratory containment. In its study of synthetic biology, Lloyd's Emerging Risks Team[16] notes that the UK-based Pirbright Laboratory, a research facility holding 5,000 strains of the foot and mouth virus (in this case, not involving synthetic DNA) experienced accidental release of viral strains in 2007 as a result of flooding and broken pipes (Lloyd's Emerging Risk Team Report 2007). Local cattle herds were subsequently infected by the escaped viral

16 Lloyd's is an insurer to businesses in over 200 countries.

strains. Natural disasters, such as flooding or an earthquake, could also lead to the unintentional release of organisms from contained systems.

In the United States a Pfizer employee became seriously ill due to improper containment of a genetically engineered virus in the laboratory. The U.S. Occupational Safety and Health Administration acknowledged that there are "many gaps" in the agency's standards for worker safety in the biotechnology industry and that "there are many things where we don't have adequate information" including new biological materials and nanomaterials. A New York Times report on the Pfizer case noted that "One study, reviewing incidents discussed in scientific journals from 1979 to 2004, counted 1,448 symptom-causing infections in biolabs, resulting in 36 deaths... But that may be a "substantial underestimation," the study's authors wrote, because many incidents are never made public" (Pollack and Wilson 2010).

A 2008 report by the U.S. Government Accountability Office concludes that there were six documented cases of unintentional releases of genetically modified organisms in the U.S. between 2000 and 2007, but "the actual number of unauthorized releases is unknown" (U.S. Government Accountability Office 2008, p. 3).

Based on recent history, commercial-scale containment of synthetic organisms is impractical, and assured containment is likely to be impossible. Much synthetic biology research currently focuses on the production of synthetic algae for biofuels production. Sapphire Energy, for example, is building a 300-acre open pond algae farm in Columbus, New Mexico, approximately three miles north of the U.S.-Mexico border. When asked about potential leaks of engineered algae, even from laboratory containment, one algae biofuels experts told the *New York Times*, "[algae] have been carried out on skin, on hair and all sort of other ways, like being blown on a breeze out the air conditioning system…" (Maron 2010). Another algae expert, a chemical engineer who founded the first algae-to-biofuel company, told the *New York Times*, "of course it's [algae] going to leak, because people make mistakes" (Maron 2010). These comments suggest that an open-pond or partially contained algae operation covering 300 acres will allow for the introduction of novel algae strains into the local environment.

Manufacturing facilities that use synthetic microbes in contained systems such as biorefineries (e.g. for fermenting biofuels and biobased chemicals), are not expected to maintain the same level of containment as biosafety accredited labs. Biorefineries are analogous to breweries, which routinely experience escapes of cultured yeast.

Some applications of synthetic organisms plan for intentional release of engineered organisms into the environment. Examples include agricultural crops modified to incorporate synthetic pathways, synthetic organisms engineered for the purpose of bioremediation (such as oil-eating microbes to consume oil from oil spills or toxic chemicals), or the use of synthetic microbes as an agricultural pesticide or herbicide (Presidential Commission

for the Study of Bioethics 2010). The fate of synthetic organisms designed to survive in the wild, and their impact on ecosystems and biodiversity, have yet to be studied.

**Potential ecological risks associated with the release of synthetic organisms**

Unlike other forms of pollution, such as chemical spills, which can be contained or cleaned up, living self-replicating organisms cannot be taken back if they are released into the environment (Snow 2010). A 2009 report points out, “even if the source of all of the parts of a synthetic microorganism are known, and every new genetic circuit understood, it would be difficult to predict in advance whether the organism would have any unexpected emergent properties.” (Rodemeyer 2009, p. 27). While engineered organisms may not have a fitness advantage in the open environment, it is also possible that they could find an ecological niche, survive and reproduce, and swap genes with other species.

Released synthetic organisms could lead to genetic contamination, threatening biodiversity and the wellbeing and livelihoods of surrounding communities Most of the organisms being engineered through synthetic biology (e.g., algae, yeast, E. Coli) naturally and regularly swap genes. There are three main mechanisms for horizontal gene transfer:

1) *Conjugation:* The transfer of DNA from one organism to another
2) *Transformation:* Free DNA in environment taken up by organism (DNA could come from dead organisms)
3) *Transduction:* DNA transfers from one organism to another by a virus (Woodrow Wilson International Center for Scholars, 2011).

The process of horizontal gene transfer has been known for some time, but a 2010 study published in *Science* documented that microbes swap genes through horizontal gene transfer at “frequencies a thousand to a hundred million times higher than prior estimates … with as high as 47% of the culturable natural microbial community confirmed as gene recipients (McDaniel 2010). Not only do microbes swap genes with each other, but organisms can swap genes between species. In one case a sea slug picked up DNA from algae, allowing it to conduct photosynthesis (Rumpho et al. 2008).

Even if engineered organisms do not survive outside of a contained facility, synthesised DNA could remain in the environment and be picked up by living organisms through transformation. In 1928, Griffith found that mice injected with a non-virulent *S. pneumonia* (a form of Streptococcus) mixed with DNA from a dead but virulent form of the bacteria were infected and died (Griffith 1928). It was later discovered that this happened when the non-virulent bacteria picked up and incorporated the DNA from dead *S. pneumonia* into its genome, turning it virulent. Concerns about waste and disposal of synthetic organisms are particularly heightened by the increasing numbers of amateur ‘DIY’ synthetic biologists now using the tools of synthetic biology in informal settings such as residential kitchens, garages and ‘hacker spaces’. (Wohlson, 2011)

Organisms engineered to produce industrial chemicals or fuels that escape confinement could also become a new class of pollutants. Algae engineered to produce oils, for example, could escape and continue producing oil in a local waterway. An organism engineered to break down sugarcane could escape and continue to consume sugar in the surrounding environment. According to the technical opinion used by the Brazilian government to approve Amyris's synthetic yeast to turn sugar into farnesene, the yeast (strain Y1979) was able to survive up to one hundred and twenty days in a vial containing soil from a local sugarcane farm. Additionally, the opinion admitted that the "presence of farnesene on the vicinity is, eventually, an additional concern…discarding [the yeast] over the soil is the most likely destination, in the short run, of this byproduct" (Anonymous, 2009).

A common industrial application of synthetic biology is the development of microbes to transform cellulose and other sugars into industrial compounds. There is concern that such organisms, if released into cellulose rich environments (soils, forests, etc.), could continue to secrete environmental pollutants. In  a parallel case when researchers added a genetically engineered *Klebsiella planticola* (a common soil bacterium that was engineered through recombinant DNA techniques to improve the fermentation of wheat to ethanol) to soil in the laboratory, the engineered microbe persisted in the soil and after three weeks significantly decreased the numbers of bacterial and fungal feeding nematodes, subsequently killing wheat plants growing in the soil (Holmes et al. 1999). The non-engineered bacterium did not have similar effects. The authors suggested that the engineered *Klebsiella planticola* had utilized plant roots and organic matter in the soil to continue producing ethanol. This case illustrates the potential ecosystem wide impacts that the introduction of novel genes and organisms can produce in the absence of proper risk assessment and mitigation strategies, particularly where microorganisms are engineered to produce an industrial compound or to use cellulose and other common sugars as a feedstock.

There is also a risk that synthetic organisms could become a new form of invasive species (Snow 2010). If an organism is engineered for hardiness – as algae grown in open ponds often are – it is possible they could survive and proliferate in an ecosystem. According to Tucker and Zilinskas, synthetic organisms could negatively impact the environment in three main ways: "First, the organism could disrupt local biota or fauna through competition or infection that, in the worst case, could lead to the extinction of one or more wild species. Second, once a synthetic organism has successfully colonized a locale, it might become endemic and thus impossible to eliminate. Third, the synthetic organism might damage or disrupt some aspect of the habitat into which it was introduced, upsetting the natural balance and leading to the degradation or destruction of the local environment" (Tucker and Zilinskas 2006, p. 35).

**The nascent field of xenobiology does not offer safe or reliable methods for biocontainment and control of synthetic organisms.**
Some observers suggest that reliable biological containment and control methods can be developed to prevent synthetic organisms from multiplying in the natural environment and to safeguard biodiversity and human health in the event of accidental release. For example, “suicide genes” or other types of self-destruct triggers could be engineered into synthetic organisms in order to limit their life spans, or organisms could theoretically be designed to depend on the presence of chemicals that are absent outside the laboratory/bioreactor, such as novel, non-natural amino acids.

Some researchers are attempting to produce unnatural molecules and architectures for the purpose of creating xenobiological systems that will theoretically function as “the ultimate biosafety tool.” The leading proponent of xenobiology describes it as an “opportunity to implement a genetic firewall that impedes exchange of genetic information with the natural world” (Schmidt 2010, p. 322). Xenobiology would operate on a genetic software program (dubbed XNA) that would be theoretically incompatible with naturally-evolved DNA – thus preventing the exchange of genetic material through horizontal gene transfer or via sexual reproduction (Schmidt 2010).

For example, in July 2011 researchers reported that they have used automated selection in the laboratory to intentionally evolve a strain of chemically-modified *E. coli* bacterium in which one of the four standard nucleotide bases, thymine, has been replaced with a synthetic base called 5-chlorouracil, a toxic chemical (Marlière 2011). In theory, the organisms that incorporated non-natural building blocks in their genome could no longer exchange genetic material with wild type organisms. Even if the DNA/XNA is not incorporated into another organism, it will still remain in the environment when the organism dies; the environmental impact of releasing self-replicating organisms with a toxic chemical in their genome has yet to be studied.

Attempts to develop methods for the biological confinement of living modified organisms is not new. In 2004 the U.S. National Research Council (NRC) published a major report on the status, feasibility and probable ecological consequences of the use of bioconfinement methods to prevent escape of genetically modified organisms (National Research Council 2004). The report concludes that “it is likely that no single method can achieve complete confinement on its own.” It also finds that the lack of quality data and science is the single most significant factor limiting the ability to assess effective bioconfinement methods, and that bioconfinement should be evaluated on a case by case basis, considering worst case scenarios and the probability of occurrence (National Research Council 2004, p. 12). The NRC report does not specifically address synthetic biology and xenobiology, and the methodology to assess the effectiveness of xenobiology methods do not yet exist. Attempts to create biological containment systems in plants indicate that such traits may represent an evolutionary disadvantage and selective pressures have led organisms to overcome intended biological constraints (Steinbrecher 2005).

Proposed forms of biological containment through alternative genetic systems are highly theoretical. No application of these synthetic biology techniques has moved beyond basic research stages and “proof of concept” experiments. Living organisms are sufficiently versatile under the pressure of natural selection; it is possible that an organism could evolve to incorporate xenobiotics into its metabolic repertoire, or to “kick out” such traits in later generations.

**There is currently no comprehensive regulatory apparatus for the oversight and governance of synthetic biology at the national or international level.** Although existing national laws and regulations may apply to some aspects of the emerging field of synthetic biology, there is no comprehensive regulatory apparatus for synthetic biology at the national or international level (Zang et al. 2011). The new and emerging field of synthetic biology is steeped in scientific uncertainty (IRGC 2010). However, the Precautionary Principle is not currently guiding the development of synthetic biology in those countries and regions that are most actively conducting R&D in the field. In recent years, self-regulation has been promoted by some scientists and industry stakeholders as the preferred approach to the governance and oversight of synthetic biology (Garfinkel et al. 2007). The U.S. President’s Bioethics Commission, as well as industry organizations, currently advocate for “prudent vigilance” as the path to responsible stewardship of synthetic biology (Presidential Commission for the Study of Bioethical Issues, 2010). The only synthetic biology-specific regulation in the U.S. today is a voluntary framework for synthetic gene manufacturers to screen customers and the synthetic double-stranded DNA sequences they request to minimize the risk that synthetic DNA could be used to create a select agent or toxin.[17]

**Many of the researchers who are most active in the field of synthetic biology do not have training in biological sciences, biosafety or ecology.** According to one of the world’s leading synthetic biologists, “…the majority of people coming into synthetic biology aren’t biologists. They’re physicists or computer scientists or electrical engineers and so they’re just of a different culture. They don’t have a lot of experience with microbiological safety. So you need to gain access or transmit knowledge across not just a generational gap, but across cultural divides” (Endy in Lentzos et al. 2009, p. 319) In addition, the de-centralized control of synthetic biology presents additional biosafety and biosecurity challenges. The tools of synthetic biology – computer designed, synthetically produced DNA – are available via mail order to virtually anyone with a laptop computer. This includes do-it-yourself (DIY) participants and “bio-hackers” who may

17 Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA. http://www.phe.gov/Preparedness/legal/guidance/syndna/Documents/syndna-guidance.pdf

have no formal training or familiarity with best practices in laboratory safety, such as proper disposal of biological waste, etc.[18]

**The Cartagena Protocol does not sufficiently cover synthetic biology and its potential impacts on biodiversity.** The Cartagena Protocol regulates the risks to biodiversity arising from the trans-boundary movement of living modified organisms (LMOs). While its definition of an LMO fully embraces the products of synthetic biology,[19] its mechanisms for regulation do not adequately cover advances in gene science since the Protocol was laid down. The Cartagena Protocol on Biosafety, its Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress, and the Nagoya Protocol on Access and Benefit-Sharing (the Protocols) require updating in light of recent scientific developments in order to ensure that the very objectives of these treaties are upheld and a technology-induced regulatory bypass is avoided.[20] It is beyond the scope of this submission to provide a comprehensive analysis of the reforms required but we briefly outline below three important areas where current rules and procedures for safe transfer, handling and use of LMOs are inadequate. We recommend that the AHTEC be charged with undertaking an analysis of the new and additional risks synthetic organisms pose as the basis for a fuller response.

**The Cartagena Protocol does not cover the virtual (digital) transfer of LMOs.**
The protocols currently apply only to the physical transfer of biological materials. It is now possible to translate the genetic code of an LMO into digital form, export this to another jurisdiction, and then 'retranslate' the digital form back into its physical form. Digital DNA sequences are electronically transferred, synthesised in vitro, and later assembled to create a viable (living) organism. In this way the protocol provisions are not triggered because no physical transfer of genetic material takes place, and yet entire DNA sequences would have been exported without prior consent,

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18 According to Jason Bobe, Harvard University, at workshop conducted by Woodrow Wilson International Center. Report from Department of Energy (DOE) – Alfred P. Sloan Foundation Workshop on "Societal Issues Arising from Synthetic Biology: What Lies Ahead" Hosted by the Woodrow Wilson International Center November 7-8, 2010 http://www.synbioproject.org/process/assets/files/6602/_draft/social_issues_synthetic_biology_report.pdf

19 Article 3(g): ""Living modified organism" means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology".

20 The Nagoya-Kuala Lumpur Supplementary Protocol applies to damage resulting from the transboundary movement of LMOs; http://bch.cbd.int/protocol/supplementary/ The Nagoya Protocol covers the fair and equitable sharing of benefits arising from access to genetic resources; http://www.cbd.int/abs/doc/protocol/nagoya-protocol-en.pdf

contrary to the protocols' intent. (Note that this gap applies equally to the products of genetic modification).

In absence of reform, virtual transfer provides a ready mechanism for evasion of the Protocols. One approach to such reform is to require those who retranslate digital code into a physical LMO to be subject to prior informed consent procedures. In essence, they would be required to apply to the government of the jurisdiction in which they are based as if they were an exporting agent seeking approval to import. This framing also covers the case where there is no identifiable sender of the code and it is simply downloaded from a website. Whether there is merit overall in alternatively or also regulating those who send the genetic code of an LMO in digital form, or post such code to a website, would require careful consideration.

**The Cartagena Protocol does not cover the transfer of constituent parts of an LMO that can be readily assembled.**

A problem common to both virtual transfer and physical transfer of synthetic organisms is the potential for export of the constituent parts (i.e., biobricks) of an LMO rather than the whole organism. Such a process would bypass the protocols' rules that at present cover only a living, and thus whole, organism. Against the assumption the Cartagena Protocol was framed under, that only viable biological material presented a risk, synthetic biology opens up the ability to export products which jointly have what we term 'latent viability'. A set of such products may together be just a few straightforward steps away from being constituted (or reconstituted) into an LMO.

Export of LMO constituent parts in such kitsets would amount to a serious evasion of the Protocols' intent. Reform in this case seems likely to involve making both exporters and importers subject to prior informed consent procedures. For importers, the process of constituting an LMO from prefabricated parts could trigger requirements similar to those for virtual transfer: they could be required to apply to the government of the jurisdiction in which they are based as if they were an exporting agent seeking approval to import. For exporters, informed consent procedures could apply to the virtual or physical transfer of biological material deemed to collectively possess latent viability. The intent would be to capture not only what is obviously a complete kitset but also assemblies that are well down the path to becoming viable and need little by way of additional components to exhibit viability.

**The Cartagena Protocol, so far, allows for the import of synthetic organisms into contained use without analysing and adapting the containment standard.**

Article 6.2 of the Cartagena Protocol waives the requirement for advance informed consent in the case where the LMO is destined for "contained use", as defined by the Party of import.[21] However, the term "contained use" is

21 "…the provisions of this Protocol with respect to the advance informed agreement procedure shall not apply to the transboundary movement of living modified organisms destined for contained use undertaken in accordance with the standards of the Party of import." Article 6.2, Cartagena Protocol on Biosafety.

defined in the Protocol as a physical facility effectively limiting the exchange with the environment. This means that an organism developed through synthetic biology may be imported into containment facilities judged adequate for genetically modified organisms but which may be unsuitable for synthetic organisms. In order to judge the effectiveness of available containment the importing country must have advance information about what is entering its territory.

As previously noted, there is general recognition that fail-safe containment of synthetic microbes is unlikely due to human error (including escape from laboratory facilities, fermentation tanks or biorefineries). Without the extension of informed consent to include the transboundary movement of synthetic organisms that are destined for contained use, Parties to the Protocols as they stand could find that organisms have been imported without prior notification and where there is no adequate containment. They could then be unprepared (and probably ill-equipped) to deal with the possibility of unintentional release of living, self-replicating organisms that may be optimized to synthesise chemical and/or natural products. The root concern is that the accidental release of a synthetic organism could result in its possible spread into new ecological niches and the emergence of new and potentially harmful properties (as discussed previously, see pp. 20-21).

A further issue raised by the exemption for contained use is the potential for agents to engage in regulatory arbitrage. If a Party has domestic standards for risk assessment that are lower than the minimum provided for in Annex III of the Cartagena Protocol, an agent residing in that country can initially import for the purpose of contained use, and then apply to release the LMO from containment under the weaker domestic procedures. In order to block such arbitrage and uphold the objectives of the Convention and its Protocols, reform is required to ensure that any agent receiving an LMO into containment without obtaining prior informed consent may only release that LMO after it has been approved under a risk assessment process at least as strong as that specified in Annex III.

As with the issues raised in the two previous sections, the solutions increasingly require that international standards are enforced at the domestic level in order to ensure effective regulation and protection – against transboundary risks to biological diversity, including human health. In each case the solutions proposed trace back to an international obligation and the objectives of the Protocols.

**The evolution of synthetic biology, genomics and chemical synthesis of DNA could profoundly alter current practices related to the conservation and sustainable use of biodiversity and rules governing access and benefit sharing.**

In the age of genomics, genetic code is proliferating and is widely accessible to anyone with a computer and Internet access. The U.S. government's GenBank provides an open access, annotated collection of all publicly

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http://bch.cbd.int/protocol/

available nucleotide sequences and their protein translations.[22] As of September 2011, genome sequences are available for 4035 genomes (completed or partially assembled); 1757 microbial genomes have been fully sequenced (including 1640 bacterial genomes and 117 archaea); an additional 5230 microbial genomes are in-progress of being sequenced and assembled.[23]

Digital DNA is the “raw material” (in silico) that enables synthetic biologists to fashion and/or re-engineer living organisms. Rather than sourcing genes from nature or gene bank samples, scientists are able to download digital DNA sequences that can be rapidly constructed by commercial DNA foundries. Mail order genes and gene sequences are now common. Thousands of microbial genomes have already been sequenced and scientists predict that within a few years it may become possible to electronically specify the genome of a complex organism and receive it via courier a few days later (however, this may not be possible for plants or animals for sometime). As gene synthesis becomes cheaper and faster, it may become easier to synthesise a microbe than to find it in nature or retrieve it from a gene bank.

Paul Oldham of Lancaster University’s ESRC Centre for Economic and Social Aspects of Genomics observes: “…the extraction of genetic data has classically depended upon the collection, taxonomic identification and storage of field samples, i.e. within herbaria. However, it is conceivable that technological innovation may one-day permit the in situ extraction of genetic material and transfer of data to electronic form without the necessity of the collection, taxonomic identification and storage of field samples” (Oldham, 2004).

Biological samples, sequenced, stored and transferred in digital form, could erode future support for biodiversity conservation, both in situ and ex situ, and create new challenges for the fair and equitable sharing of benefits arising from the utilization of genetic resources, one of the three objectives of the CBD.

The Nagoya Protocol on Access and Benefit Sharing[24] does not cover digital sequences and products derived from natural sequences using synthetic biology tools – providing a potential mechanism for evasion of the Protocol.

Material transfer agreements and contracts governing access to and exchange of germplasm may also be affected. Researchers who obtain germplasm samples from gene banks, such as those operated by the

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22 http://www.ncbi.nlm.nih.gov/genomes/lproks.cgi

23 http://www.ncbi.nlm.nih.gov/genomes/lproks.cgi

24 Adopted by the Conference of the Parties to the Convention on Biological Diversity at its tenth meeting on 29 October 2010 in Nagoya, Japan, and currently open for signature until 1 Feb 2012.

Consultative Group on International Agricultural Research, are currently required to sign a legally binding Material Transfer Agreement.[25] However, the same researcher can obtain digital DNA sequences from GenBank with no legal strings attached, unless the accession is claimed separately by a patent.

At the request of the Ad Hoc Open-ended Working Group on Access and Benefit-sharing, an informational document was prepared to examine the historical concept of genetic resources and its continued evolution in the context of rapidly emerging technologies – including synthetic biology.[26] The report notes the challenges of maintaining a broad and dynamic understanding of the concept of genetic resources in light of rapidly developing technologies:

“If the concept of genetic resources is understood only narrowly, in senses related to the original or current state of knowledge, the ABS system may not be able to capture the future potential value of genetic material, not least when it is used in or as a basis for synthetic biology or other new bio-economic technologies. An International ABS Regime could maintain a broad and dynamic understanding of the concept of genetic resources” (Schei and Tvedt 2010).

25 A Material Transfer Agreement [MTA] is a contract that governs the transfer of research materials from one party to another when the recipient intends to use them for his or her own research purposes. The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives.

26 UNEP/CBD/WG-ABS/9/INF/1

## Part 3: The Potential Impacts of Synthetic Biology on Biodiversity and Food and Livelihood Security, especially in the developing World

Applications of synthetic biology pose enormous potential impacts on biodiversity and the livelihood and food security of smallholder farmers, forest-dwellers, livestock-keepers and fishing communities who depend on biodiversity, especially in the developing world.

The "bioeconomy" broadly refers to economic activities relating to the invention, development, production and use of biological products and processes – including synthetic biology (OECD 2011). With advances in metabolic pathway engineering, synthetic biologists are turning microbial cells into "living chemical factories" that can be induced to manufacture substances they would not produce naturally. Microbial production processes depend on fermentation, and fermentation requires sugar feedstocks (that is, biomass). Biomass is defined as "the biodegradable fraction of products, waste and residues from agriculture (including vegetal and animal substances), forestry and related industries, as well as the biodegradable fraction of industrial and municipal waste."[27]

While some observers believe that the 21st century bioeconomy may greatly enhance environmental sustainability and boost productivity of agriculture and industrial processes, many have overlooked the demand for biomass that will accompany bio-based production processes, and the subsequent impact on land use and biodiversity.

1) **To date, no studies have systematically examined the increased demand for biomass, and the subsequent impact on biodiversity, that may result from the provision of biomass feedstocks to fuel industrial-scale fermentation by engineered, synthetic organisms.**

Commercial applications of synthetic biology will depend on access to bio-based production processes fueled by biomass. With an estimated 86% of global biomass stored in the tropics or subtropics, developing countries are already being tapped as the major source of biomass to supply industrial-scale feedstock for fermentation tanks and biorefineries (ETC Group, 2010). Synthetic biology companies such as Amyris, Solazyme and LS9, for example, are basing operations in Brazil precisely because of the availability of sugar cane feedstocks; GlycosBio will locate its production facilities in Malaysia because of low-cost, oil palm feedstocks. BioArchitecture Lab is establishing macroalgae growing in Chile as a feedstock source for its synthetic biology operation. In September 2011 the CEO of one synthetic biology company told *Business Week*, "I'm searching the world for cheap sugars" (Martin 2011).

Current and near-term synthetic biology applications are *not* limited to biofuel production. With billions of dollars of public and private investment (including the world's largest energy, chemical and agribusiness

27 EU Directive 2001/77/EC (RES-E).

corporations), the vision is to use biomass as a feedstock for designer microbes that will be used to transform plant cellulose into fuels, chemicals, plastics, fibers, pharmaceuticals and more. How much will demand for biomass increase as a result of synthetic biology applications? Estimates are not available, but the amount of biomass required to operate a single biorefinery suggests that the biomass requirements for industrial-scale production of synthetic organisms could have profound implications for land-use and land conversion. For example:

- Dupont is using synthetically altered yeast to ferment corn sugars that produce propanediol, a precursor to the company's synthetic thermoplastic polymer fibre, marketed as Sorona. Dupont's industrial scale bio-refinery based in Tennessee (USA) requires 40,000 acres of maize (16,190 ha) to produce 100 million lbs. (over 45 million kg) of Sorona (Anonymous 2006).

- Amyris, Inc. has used synthetic biology to engineer the metabolic pathway of yeast to produce a molecule called farnesene – an essential building block for a wide range of chemical products (detergents, cosmetics, perfumes and industrial lubricants and transportation fuels). Amyris has already secured production capacity in Brazil; according to the company's plan, the facility will be capable of producing farnesene from up to two million tons of crushed sugarcane annually (Anonymous 2010).

- Mascoma selected the site of its commercial-scale biorefinery to produce cellulosic ethanol (fueled by wood chips, bark and other forest products or by-products) because of it close proximity to approximately 8.3 million acres of timberlands in northern Michigan (USA) (Brady, 2011).

- According to the U.S.-based Biotechnology Industry Organization, a minimum of 500,000 acres of cropland is currently required to sustain a commercial-scale biorefinery (Biotechnology Industry Organization, 2006).

Proponents of synthetic biology point out that future applications will not necessarily require crop-based feedstocks, but will use biomass from agricultural or forestry "waste" or non-food sources such as fast-growing algae that will require a fraction of the land currently required for making biofuels derived from maize, soybean, oil palm or cellulose. However, initial environmental impact assessment of cellulosic and algal fuels points to significant requirements for additional water and nutrients to maintain soil fertility in agricultural systems or sustain algal growth:

Agricultural Waste: Removal of remnant biomass from agricultural soils (e.g., corn stover, rice husks) for conversion into fuels or other compounds will lead to a decline in soil fertility and structure and increased requirement for fertilizer to maintain yields. Studies have shown that US agricultural soils for example have already lost between 30 and 50% of their organic carbon since

cultivation began (little over a century in many cases). A 2009 paper shows that removing any level of corn stover (unharvested stalks) that are usually ploughed back into fields in US Agriculture would further lower soil carbon levels as well as reduce yield in subsequent years (Blanco-Canquia, 2009)[28]. In a 2007 paper published by *Agronomy Journal*, agronomists associated with the US Department of Agriculture confirmed that the need to maintain organic soil carbon just for maintaining fertility and soil structure, would prove a considerable constraint on the availability of cellulosic biomass for fuels (Willhelm, 2007). In this way extraction for cellulosic matter may still 'compete' with food production since the result of diminished soil fertility would likely be increasing demand and pushing up prices of fertilizer. Global use of fertilizers rose 31% between 1996 and 2008 due in part to biofuel plantings (Bradsher and Martin, 2008) however estimates by fertilizer industry analysts show that if 40% of corn stover is also removed from US fields for refining into fuel than making up the nutrients removed in that portion would contain boost annual US sales of Nitrogen, Phosphate and Pottasium fertilizers by 20%, 14% and 110% respectively.(Fixen, 2009) Increased fertilizer use is associated with increased nitrous oxide ($N_2O$)emissions from agriculture – a potent greenhouse gas. ($N_2O$ has a global warming potential 298 times the carbon dioxide equivalent over a 100-year timeline (IPCC 2007).

Algae: Algal production is mostly targeted towards shallow open pond systems or closed bioreactors deployed over extensive areas of desert requiring energy intensive cycling of water and continuos input of fertilizers. In a recent life-cycle analysis of algal biofuels researchers concluded that algae production consumes more water and energy than other biofuel feedstocks such as canola, corn and switchgrass and with higher greenhouse gas emissions (Clarens 2010).

2) **New, natural substitutes manufactured by organisms that are modified with synthetic DNA have the potential to adversely impact traditional commodity exports and displace agricultural workers.**

While governments, industry and scientists in OECD countries have been quick to point out the potential contributions of synthetic biology to environmental sustainability and development in the global South, the potential disruptive impacts of synthetic biology on developing economies,

28 The paper *Corn Stover Removal for Expanded Uses Reduces Soil Fertility and Structural Stability*, by Humberto Blanco-Canquia and R. Lal, published in Soil Sci Soc Am J. 73: 418-426 (2009) documented the 4 year impacts of a systematic removal of stover on selected soil fertility indicators and structural stability across three contrasting soils in Ohio. Complete stover removal reduced the total N pool by, on average, 820 kg / ha in the silt loams. It reduced available P by 40% and the cation exchange capacity. Exchangeable $K^+$ decreased by 15% on the silt loams for stover 75% removal and by 25% under complete removal.

particularly least developed countries that depend on agricultural commodities, have received far less attention. History shows that there will be a push to replace high-value ingredients and commodities with cheaper raw materials. Many natural compounds, (i.e., natural oils and aroma chemicals) are sourced from plants originating in the tropics and sub-tropics. Synthetic biology companies are now partnering with the world's largest flavor and fragrance companies to develop a commercially viable biosynthetic route to express natural plant genes in engineered microbes. In the words of one synthetic biologist, "We ought to be able to make any compound produced by a plant inside a microbe" (Specter 2009). For example, Amyris, Inc. partners with multinational firms Givaudan and Firmenich, and Swiss-based Evolva is working with International Flavors and Fragrances to develop "sustainably-sourced" ingredients for this market.[29] The estimated value of the global market for flavor and fragrance compounds was $20 billion in 2007 (Hansen et al 2009). Commercial viability depends on whether synthetic microbes can produce high-quality natural chemicals at lower cost than current processes.

**Natural compounds being developed or commercialized in production systems based on synthetic organisms**

| Natural compound | Institution/Firm developing synthetic biology production | Stage of development | Natural product sourced from | Synthetic biology production based in | Market size (estimates) |
|---|---|---|---|---|---|
| Artemisinin (*Artemisia annua)* | Amyris / Sanofi Aventis; Riken Institute | To be commercialized 2012 by Sanofi | China, Vietnam, Cameroon, Ethiopia, Kenya, Mozambique, Tanzania, Uganda and Zambia | USA, Czech Republic, South Africa, Japan | Global supply and demand for artemisinin ~ 120-140 MT |
| Jojoba Oil (*Simmondsia chinensis)* | LS9 Inc. | Pre-commercial | Argentina, Australia, Chile, Egypt, India, Israel, Mexico, Peru, South Africa, USA | USA | ~5,000 tons of jojoba is used in personal care products worldwide |
| Liqourice (*Glycyrrhiza glabra)* | RIKEN Institute, Tokiwa Phytochemical Co. | Proof of principal | India, Spain, Iraq, Iran, Turkey, Russia, China, Mongolia, Kazakhstan | Japan | 20,839 tons of liquorice dried extract (2004) |
| Palm Oil (*Elaeis species*) | Solazyme/Unilever, Synthetic Genomics Inc./ Genting Group | R&D | Malaysia, Indonesia, Thailand, Colombia, Benin, Kenya, Ghana | USA | 48 million tones of palm oil (accounts for 30% of global production of |

29 Details available on company websites: http://www.amyris.com/markets/chemicals/flavors-and-fragrances ; http://www.evolva.com

| Natural compound | Institution/Firm developing synthetic biology production | Stage of development | Natural product sourced from | Synthetic biology production based in | Market size (estimates) |
|---|---|---|---|---|---|
| | | | | | oils and fats) |
| Natural Rubber (*Hevea brasiliensis*) | Amyris/Michelin; Genencor/Dupont/ Goodyear Tire & Rubber Co.; GlycosBio/ Bio-XCell Sdn Bhd (Malaysia); | To be commercialized 2013 (Genencor) or 2014 (GlycosBio) | Thailand, Malaysia, Indonesia, India, Vietnam, China, Sri Lanka, Cambodia, Papua New Guinea, Philippines | USA, Malaysia | 8.9 million metric tons (demand for isoprene per annum) |
| Pyrethrin (*Tanacetum cinerariaefolium)* | Wageningen University | R&D | Kenya Tanzania, Australia Japan Dalmatia Ecuador Rwanda, Uganda, Papua New Guinea | Netherlands | 2850 tons of pyrethrum flowers harvested worldwide (2000) |
| Stevia (*Stevia rebaudiana)* | Evolva Inc., Vineland Research | Pre-commercial, R&D | Paraguay, Brazil, Argentina Uruguay, Israel, China, Thailand, United States | Switzerland, USA, Canada | worldwide sales of stevia extract 3,500 tons (2010) |
| Taxol *(Taxus brevifolia)* | University of California Berkeley | Proof of principal | USA/Canada | USA | N/A |
| Vanilla (*Vanilla planifolia*) | Evolva, Inc. | Scale-up. To be commercialized 2014 | Madagascar, Comoros, Reunion, Indonesia, French Polynesia, Mexico, China, Dem. Rep. of Congo, Malawi, Uganda, Tonga | Denmark, Switzerland | Approx. US$200 million. |
| Vinblastine (*Catharanthus Roseus*) | MIT (NB: Rosy periwinkle is being used as a plant chassis for synthetic biology – instead of microbes) | R&D | Madagascar, China, India, Israel | USA | ~1000 tonnes exported from Madagascar per annum (FAO, 2003) |

Commercial applications of synthetic biology's designer organisms have the potential to de-stabilize traditional commodity markets, disrupt trade and eliminate jobs. Worker-displacement brought on by commodity-obsolescence, or new synthetic substitutes with qualities that are deemed "equivalent" to products sourced in nature, could have enormous impacts on agricultural

workers in the developing world, especially those who do not have the ability to respond to sudden demands for new skills or different commodities. Some point out that synthetic biology tools will offer potential for developing countries to innovate, diversify and add value to natural commodities. It is too early to predict with certainty which commodities or agricultural workers will be affected and how quickly. The case studies presented below offer a glimpse of the potential impacts of synthetic biology on tropical, plant-based commodities in developing countries.

**Case Study 1: Vanillin and Synthetic Biology**

Vanillin – the world's most popular natural flavor – is originally sourced from the cured seed pod of the vanilla orchid (*Vanilla planifolia*). Production of natural vanillin from the orchid's seed pod is time consuming and labour-intensive: 1 kg of vanillin requires approximately 500 kg of vanilla pods and hand-pollination of approximately 40,000 flowers (Hansen et al 2009). Natural vanillin sells for $1,200 - $4,000 per kg. The world market for naturally-sourced vanillin is approximately $200 million per annum. Worldwide, an estimated 200,000 people are involved in the production of about 2,000-3,000 MT of cured vanilla beans per annum.[30] Madagascar and other island nations in the Southwest Indian Ocean (Comoros, Reunion) historically account for around three-quarters of the world's vanilla bean production. Export earnings in the region are highly dependent on vanilla bean cultivation. Beyond its economic benefits, the vanilla cropping system contributes to the maintenance of agro-forestry areas. An estimated 80,000 families cultivate vanilla orchids in Madagascar on approximately 30,000 hectares. In Comoros, an estimated 5,000-10,000 families depend on vanilla bean production. Approximately 4,000 farm families in indigenous communities of Mexico cultivate vanilla orchids; approximately 8,000 families in Central Africa (Uganda, Democratic Republic of Congo, Tanzania) depend on vanilla bean production. In recent years Indonesia and China have become major vanilla bean producers; other vanilla bean producers include: French Polynesia, Malawi, Tonga, Turkey, India.

International trade in natural vanilla is characterized by extreme volatility. Due to the high quality of naturally sourced vanilla beans, however, artificial vanillin flavouring has failed to eliminate the demand for high-priced natural vanillin.

The production of artificial vanilla is not new. Due to the high cost of natural vanilla, less than 1% of the global production of vanillin is derived from cultivated vanilla pods. Most artificial vanillin is synthesised using chemically-treated lignin derived from wood pulp, a process involving sodium hydroxide, or with other chemical solvents and sells for $15 per kg – a tiny fraction of the cost of naturally-sourced vanilla. (Lignin is a complex chemical

30 Personal communication with Michel Grisoni, CIRAD (Centre de coopération internationale en recherche agronomique pour le développement), based in Reunion. All estimates for vanilla production and agronomic practices provided by Michel Grisoni.

compound derived from woody biomass.) However, due to the high quality of naturally sourced vanilla beans, artificial vanillin has thus far failed to capture the high-end market for natural vanilla.

In 2010, Switzerland-based synthetic biology company, Evolva, entered a 4-year agreement with the Danish government's Council for Strategic Research to develop a commercially viable and environmentally acceptable production route for the microbial production of vanillin. Scientists have already constructed a yeast-based fermentation route to both vanillin and other vanilla flavour components. A 2009 publication by Evolva researchers describes the creation of a de novo pathway to produce vanillin from glucose in two yeast strains; the new pathway combines bacterial, mold, plant and human genes. (Hansen et al. 2009). The target market for Evolva's fermented vanillin is an estimated US$360 million (personal communication with Evolva CEO, Neil Goldsmith, 5 October 2011).

According to Evolva, the company is already producing vanillin in engineered yeast at a price that is competitive with higher priced artificial vanillin. The company believes that vanillin produced via synthetic biology is more environmentally sustainable because it does not involve the corrosive chemical process used to produce artificial vanillin. Evolva will scale up the process in 2012 and plans to launch commercially in 2014.

At this early stage, it is not possible to predict if Evolva's fermented vanillin could replace some portion of the market for natural vanilla sourced from cured vanilla beans. The company claims that it does not expect to capture the market for naturally sourced vanilla. The CEO of Evolva, Neil Goldsmith, acknowledges that the company's fermented vanillin is not equivalent to the cured vanilla bean, but he says that the taste profile of vanillin produced by engineered yeast is more complex and closer to the natural vanilla flavor (personal communication with Evolva CEO, Neil Goldsmith, 5 October 2011). Evolva intends to make not just vanillin, but other molecules involved in the complex flavour profile of natural vanilla. Commercial viability ultimately depends on many factors. However, if Evolva succeeds in producing a high-quality vanillin flavour that can be scaled-up at a fraction of the cost of natural vanilla, it has the potential to provide a bio-based substitute for some or all of the natural vanilla bean flavour market.

**Case Study 2: Rubber (isoprene) and Synthetic Biology**

Outside of the biofuels category, rubber is the tropical, plant-derived product that is receiving the most attention by synthetic biology companies. The focus is on *isoprene* – the molecule that is a crucial building block for making artificial rubber. The gene encoding *isoprene* has been identified only in plants such as rubber trees (*hevea*). In 2010, DuPont subsidiary, Genencor, announced that it has used synthetic biology to construct a gene that encodes the same amino acid sequence as the plant enzyme, which is optimized for expression in an engineered *Escherichia coli.* DuPont refers to its product as "BioIsoprene." The goal is to manufacture BioIsoprene cheaply and in commercial-scale quantities via fermentation. The global demand for

isoprene is an estimated 850,000 metric tons per year.[31] Aside from synthetic rubber for the manufacture of tyres, isoprene is used in the production of many industrial products, such as surgical gloves, golf balls, adhesives, etc.

Today, Asia is by far the largest producer of natural rubber. In 2010, global natural rubber production was 10.4 million metric tons. Five Asian countries accounted for 83% of all natural rubber produced worldwide. According to the International Rubber Study Group 80% of all natural rubber is produced by small holders who farm an average 1 to 2 hectares.[32] Globally, an estimated 20 million small holder families rely on natural rubber for their livelihood. For the leading four exporters (Thailand, Indonesia, Malaysia, Vietnam), natural rubber exports were valued at US$25 billion in 2010.

**Top 5 Natural Rubber Producers**

| **Country** | **Natural Rubber Production (million MT)** |
|---|---|
| Thailand | 3.3 |
| Indonesia | 2.7 |
| Malaysia | 0.9 |
| India | 0.9 |
| Vietnam | 0.8 |

Source: International Rubber Study Group

The development of artificial substitutes for plant-derived natural rubber date back over a century. Synthetic rubber is typically made from chemical synthesis of petroleum-derived isoprene. Synthetic biology companies are now competing to produce a cheaper version of isoprene in synthetic organisms. The goal is to reduce the tyre industry's dependence on petroleum-derived synthetic rubber, and, perhaps, to capture some portion of the market for natural rubber.

Three commercial teams are using synthetic biology to manufacture isoprene in microbial cell factories via fermentation:

- Genencor (now owned by DuPont) has been partnering with Goodyear Tire & Rubber since 2007 to develop BioIsoprene. Genencor predicts that its product will reach the commercial market in 2013.
- In September 2011 Amyris, Inc. announced a partnership with French tyre manufacturer Michelin to develop and commercialize isoprene.
- Texas-based GlycosBio announced in May 2010 a collaboration with Malaysia's Bio-XCell Sdn Bhd to build a biorefinery with a planned 20,000 tonne/year capacity to produce isoprene using glycerine (derived from oil palm) as a feedstock. The company plans to produce bio-isoprene for commercial rubber applications in 2014.

The tyre industry is the driving force behind changes in demand for natural

31 http://www.glycosbio.com

32 2010 statistics on natural rubber production and exports provided by the International Rubber Study Group, Singapore. http://www.rubberstudy.com/

rubber. Although natural rubber is more easily replaced by synthetics in non-tyre applications, natural rubber is still a vital – and thus far irreplaceable – component in tyres. More than 60 percent of all natural rubber is used for tyres. (The content of tyres is typically 50% natural rubber.)

BioIsoprene has already been used to manufacture prototype tyres: according to a report in *Industrial Biotechnology*, "current state-of-the-art technology has resulted in production, recovery, polymerization, and manufacture of tires with the isoprene component produced via fermentation. Continued improvements in both the cell factory and the production process are being actively pursued (Whited et al. 2010). Genencor predicts that its product will reach the commercial market in 2013.

It is too early to predict if bio-isoprene has the potential to capture a portion of the market for natural rubber. However, scientists who are working on BioIsoprene indicate that the product "has the potential to provide a large-volume alternative to Hevea natural rubber and petroleum-derived isoprene" (Erickson et al. 2011).

**Case Study 3: Artemisinin and Synthetic Biology**

The key ingredient in the world's most effective drug treatment for malaria – artemisinin – comes not from high-tech pharmaceutical research, but is extracted from an ancient medicinal plant, *Artemisia annua,* commonly known as sweet wormwood (Dalrymple, 2008). According to the World Health Organization (WHO), artemisinin-based combination therapies (ACTs) provide the most effective treatment against malaria. WHO requires that artemisinin be mixed with other malaria drugs (ACTs) to prevent the malaria parasite from developing resistance.

Today the pharmaceutical industry sources natural artemisinim from thousands of small farmers who grow *Artemisia annua* in China, Vietnam, Kenya, Tanzania, India, Uganda, Gambia, Ghana, Senegal and Brazil. In East Africa, an estimated 1,000 small-scale farmers (average 0.3 hectares) and 100 larger scale farmers (averaging 3 ha.) grow Artemisia (Heemskerk, 2006). However, the global supply of natural artemisinin has experienced boom and bust cycles and ACT drugs are priced out of reach for poor people. Fewer than 15% of under-five African children with malaria fever received ACT treatment in countries surveyed in 2007 and 2008 (Dharani, et al. 2010). Because of the increased demand for Artemisia and the reinvigoration of anti-malaria campaigns, The Royal Tropical Institute of the Netherlands predicted in 2006 that Artemisia cultivation would grow to approximately 5000 smallholders and 500 larger-scale farmers.

**Synthetic Biology Route:** In 2006, Professor Jay Keasling of the University of California-Berkeley and 14 collaborators announced they had successfully engineered a yeast strain to produce artemisinic acid, a precursor to the production of artemisinin (Keasling, 2006). Supported by a $42.5 million grant from the Bill and Melinda Gates Foundation, the researchers achieved the complex feat of engineering the metabolic pathway of a yeast with 12

new synthetic genetic parts (Withers and Keasling 2007). The microbe behaves like a miniature factory to produce artemisinic acid, and a chemical process is then used to convert artemisinic acid to artemisinin. In 2008, Amyris granted a royalty-free license for its synthetic yeast to Sanofi-aventis for the manufacture and commercialization of artemisinin-based drugs, with a goal of market availability by 2013.[33] The companies assert that the new technology will diversify sources, increase supplies of high-quality artemisinin and lower the cost of ACTs. If commercial scale-up is successful, a substantial portion of the world's future supply of artemisinin could be sourced from microbial factories instead of the sweet wormwood plant.

Malaria, a preventable and curable disease, is the fifth highest cause of death from infectious diseases globally and second in Africa, after HIV/AIDS. Everyone agrees that malaria drugs must be accessible and affordable to all who need them. But some researchers ask if sustainable and de-centralized approaches for addressing malaria and increasing supplies of artemisinin are being neglected in favor of high-tech pursuits of synthetic microbes (Heemskerk et al. 2006; ETC Group 2007). If microbial production of synthetic artemisinin is commercially successful, pharmaceutical firms will benefit by replacing a diverse set of small suppliers with one or two production factories. The Royal Tropical Institute notes that, "pharmaceutical companies will accumulate control and power over the production process; artemisia producers will lose a source of income; and local production, extraction and (possibly) manufacturing of ACT in regions where malaria is prevalent will shift to the main production sites of Western pharmaceutical companies" (Heemskerk et al. 2006)

The Royal Tropical Institute of the Netherlands observes that current shortages of artemisia could be met solely by increasing cultivation of wormwood, especially in Africa. "From a technical point of view it is possible to cultivate sufficient artemisia and to extract sufficient artemisinin from it to cure all the malaria patients in the world. An ACT could be made available at an affordable price within just 2-3 years" (Heemskerk et al. 2006, p. i). The report estimates that between 17,000-27,000 hectares of Artemisia annua would be required to satisfy global demand for ACT, which could be grown by farmers in suitable areas of the developing world. Indeed subsequent to the Royal Tropical Institute's report, farmers planted tens of thousands of additional hectares and in 2007 the artemisinin market became saturated with supply. Prices crashed from more than $1,100 per kilogram to around $200 per kilogram driving 80 processors and many small farmers out of business. As a result availability once again dropped below demand (van Noorden 2009). The 2007 production spike demonstrated the feasibility of meeting world demand for artemisinin with botanical supplies. The international drug-purchasing facility, UNITAID, subsequently established the Assured Artemisinin Supply System (A2S2) initiative to provide loans and supply chain investment to increase the artemisia harvest to sustainable

33 Details available on Amyris website: http://www.amyris.com

high levels.[34] In 2011 artemesinin production from harvested crops was estimated at between 150-170 million tones – close to 2007 levels. According to A2S2, “The present view is that artemisinin supply will be close to matching demand for 2012” (A2S2 2011).

The Netherland’s Tropical Institute’s report warns that the prospect of synthetic artemisinin production could further de-stabilise a very young market for natural artemisia, undermining the security of farmers just beginning to plant it for the first time: “Growing Artemisia plants is risky and will not be profitable for long because of the synthetic production that is expected to begin in the near future” (Heemskerk et al. 2006, pp. i-ii.).

Traditional medicinal plants offer enormous potential for new anti-malarial treatment, but few resources have been devoted to their development. A 2010 report by the World Agroforestry Centre notes that over a thousand plant species are identified by traditional healers as effective in the prevention and/or treatment of one or more of the recognized symptoms of malaria. Among these, traditional medical practitioners, rural communities and scientists have described 22 tree and shrub species that have potential for further study and development as crops by smallholders in East Africa (Dharani et al. 2010).

## Part 4: Additional Concerns Related to Synthetic Biology and Biodiversity

**Biosecurity and Bioweapons:** There is concern about the potential misapplication of synthetic biology for hostile uses. Rapid and inexpensive construction of long strands of synthetic DNA enables production of known pathogens in the laboratory. In 2005 scientists recreated the previously extinct 1918 influenza virus that killed 20-50 million people in the early 20th century. In October 2011 researchers reported that they used DNA extracted from victims of the Black Death – the 14th century plague that killed 50 million people – to reconstruct a draft sequence of the bacterium genome, *Yersinia pestis* (Bos et al. 2011). The researchers aim to eventually modify a living plague bacterium so that its genome is identical to that of the Black Death pathogen – a microbe that could be handled only in high-level biosecurity labs (Wade, 2011). Meanwhile that sequence is now freely available on the internet and feasible to reconstruct through synthetic biology. One DNA synthesis company, Blue Heron Biotechnology, has reported receiving a request for DNA sequences encoding a plant toxin, and a separate request for part of the smallpox virus (the requests were rejected) (Wade 2007). The 1972 Biological and Toxin Weapons Convention (BWC) implicitly prohibits the synthesis of known or novel microorganisms for hostile purposes. Tucker and Zalinskas note that the Convention does little to prevent the deliberate misuse of synthetic biology for hostile purposes

34 http://www.a2s2.org/

because: 1) there are 19 states which have neither signed nor ratified the BWC (as of October 2010);[35] 2) it lacks formal verification mechanisms; 3) it does not bind non-state actors (Tucker and Zalinskas 2006). Guidelines for screening DNA synthesis have been formulated by the U.S. Department of Health and Human Services. These are voluntary and apply only to double-stranded DNA. The voluntary standards have been criticized by some researchers as ineffective in addressing security risks (IRGC 2010).

**Intellectual Property:** There is concern that intellectual property claims on the products and processes of synthetic biology could inhibit basic research, restrict access to information needed for effective risk assessment and concentrate ownership and control in the hands of large, transnational enterprises. Patents have already been granted on many of the products and processes involved in synthetic biology. Examples include: 1) patents on methods of building DNA strands; 2) patents on synthetic cell machinery such as modified ribosomes; 3) patents on genes or parts of genes represented by their sequencing information; 4) patents on engineered biosynthetic pathways; 5) patents on new and existing proteins and amino acids; 6) patents on novel nucleotides that augment and replace the letters of DNA.

35 http://www.unog.ch/80256EE600585943/(httpPages)/04FBBDD6315AC720C1257180004B1B2F?OpenDocument

**Recommendations**

**We recommend that SBSTTA, in the development of options and advice on the new and emerging issue of synthetic biology for the consideration of COP11, consider the following actions/recommendations:**

**Recommended Actions under the Convention on Biological Diversity**

- Parties to the Convention on Biological Diversity, in accordance with the precautionary principle, which is key when dealing with new and emerging scientific and technological issues, should ensure that synthetic genetic parts[36] and living modified organisms produced by synthetic biology are not released into the environment or used commercially until there is an adequate scientific basis on which to justify such activities and due consideration is given to the associated risks for biological diversity, also including socio-economic risks and risks to the environment, human health, livelihoods, culture and traditional knowledge, practices and innovations.

- As first steps in addressing these tasks Parties should submit views and national experiences and identify gaps in the governance of synthetic genetic parts and living modified organisms produced by synthetic biology as developed for release or commercial use to the Executive Secretary. Parties should request the Executive Secretary to consolidate the submissions as a basis for further work and convene an Ad-hoc Technical Expert Group which is regionally balanced and comprises all the necessary fields and backgrounds to make a comprehensive assessment, i.e. including molecular biology, ecology, environmental sciences, socio-economic and legal expertise, and also including indigenous peoples, local communities, civil society representatives, farmers, pastoralists, fisherfolk and other stakeholders with the mandate to:

  i) Analyse the adequacy of existing assessment frameworks and identify gaps in knowledge and methodologies for assessing the potential negative impacts of synthetic genetic parts and living modified organisms produced by synthetic biology on biodiversity and the environment.

  ii) Assess the impact on traditional knowledge, practices and innovations, customary law, human rights and livelihoods, including customary use of biological diversity by indigenous peoples and local communities, farmers, pastoralists and fisherfolk that may ensue from the appropriation of land, sea and biomass and replacement of natural compounds by industrial production systems that utilize synthetic

36 Further analysis is required to determine which synthetic genetic parts should be covered under this proposal.

genetic parts and living modified organisms produced by synthetic biology.

- Acknowledging the model character of Article 14 of the Cartagena Protocol on Biosafety which deals with Impact Assessment and Minimizing Adverse Impacts of products of modern biotechnology, Parties should adopt legal, administrative and policy measures regarding environmental impact assessment of proposed synthetic biology projects that may have significant adverse effects on biological diversity. This should include synthetic genetic parts and living modified organisms produced by synthetic biology intended for release into the environment as well as those destined for contained use, due to the fact that effective containment in the context of synthetic biology may require updating and upgrading of the containment facilities.

- In line with decision V.5 III, The Conference of the Parties should recommend that, in the current absence of reliable data on biocontainment strategies based upon synthetic biology, including xenobiology, mirror biology, alternative nucleotides or other synthetic biology approaches, without which there is an inadequate basis on which to assess their potential risks, and in accordance with the precautionary principle, products incorporating such technologies should not be approved by Parties 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. In order to enhance the capacity of all countries to address these issues, Parties should widely disseminate information on scientific assessments, including through the clearing-house mechanism, and share their expertise in this regard;

- The Conference of the Parties should initiate the development of a mechanism, treaty or protocol to enable more rapid assessment of emerging technologies such as synthetic biology where they are relevant to the conservation and sustainable use of biological diversity and fair and equitable sharing of genetic resources. Such a mechanism, treaty or protocol, based on the precautionary principle, should provide for the anticipatory evaluation of societal, economic, cultural as well as environmental and health impacts of emerging technologies and sharing of information between parties and other stakeholders

**Recommended Actions under the Cartagena Protocol on Biosafety and the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress**

- Acknowledging the importance of complying with the objectives and articles of the Convention when faced with rapid scientific and technological innovations, the Conference of the Parties should invite the Parties to the Cartagena Protocol on Biosafety and the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to:

i) Consider extending requirements for advance informed agreement and risk assessment procedures to synthetic genetic parts in order to cover gaps that otherwise permit evasion of the rules agreed under the protocols. One gap arises from new techniques that make it possible to import DNA sequences over the internet, such that no physical transfer takes place. A second gap arises from related techniques that allow an LMO to be imported as a set of parts ready to be reconstituted, rather than a whole viable organism. These threats to the objectives of the protocol could be addressed by extending advance informed agreement rules so that they also apply to:

- - Agents that construct an LMO, whether from electronic code or genetic parts; and

- Agents that export genetic parts (such as biobricks) that are "latently viable" (parts deemed to posses sufficient latent potential to form or promote the formation of a viable organism).

- ii) Consider excluding from the ‘contained use’ provisions, synthetic genetic parts and living modified organisms produced by synthetic biology, in order to address the new containment challenges they pose - at least until effective containment methods can be demonstrated. Thus the Article 6.2 exemption from having to obtain advance informed agreement for contained use would not apply.

[iii) Consider the case in which an agent imports an LMO into containment (without obtaining advance informed agreement) and subsequently seeks to take it outside containment, that such an agent be then required to obtain an approval from the domestic regulator based on a risk assessment process that is at least as strong as set out in Annex III of the protocol. This is to avoid an agent being able to gain advantage in jurisdictions where the domestic requirements are weaker than apply under Annex III.

**Reccomended Actions under the Nagoya Protocol on Access and Benefit Sharing**

- The Conference of the Parties should further invite the parties to the Nagoya Protocol on Access and Benefit Sharing to consider extending agreements on access and benefit sharing to cover digital genetic sequences and products derived from natural sequences using synthetic biology tools such as directed evolution techniques.

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