Review Article

Synthetic Biology and International regulatory law

Abstract

Synthetic biology is a multi-disciplinary area that combines biology with engineering, physics, mathematics, chemistry, and computer science for designing or creating new life forms. The main approaches of synthetic biology are creating Biobricks, metabolic pathway engineering, whole-genome synthesis, Protocell engineering, and Xenobiology. Synthetic biology involves different fields; pharmaceutical, energy production, chemical production, biosensor, and environmental protection. Even though it has many applications, it also has biosafety, biosecurity, and bioethics risk concerns. In order to elevate these dual-use risks, strong regulatory laws must be established. Some of the applications and products of synthetic biology are included under the Cartagena protocol as living modified organisms. The transboundary movement of living modified organisms of synthetic biology is governed by the advance informed agreement of the protocol. The dual-use technology with regard to synthetic biology products is governed by laws ratified in the Biological weapon convention. The Nagoya protocol, trade-related aspects of intellectual property rights, and other regulatory frameworks are also used for synthetic biology. But synthetic biology is an emerging technology and the international laws have no specific laws to inform all aspects of synthetic biology. The objective of this review is to describe the applications and risks of synthetic biology, to assess the regulatory laws on synthetic biology.

Key words: Biobricks, Biofuel, Biological Weapon Convention, Biosensor, Cartagena protocol, Genome synthesis, Pharmaceutical product, Synthetic biology, Xenobiology

Acronyms

AHTEG- Ad Hoc Technical Expert Group

AIA- Advance Informed Agreement

BWC- Biological Weapon Convention

CBD- Convention on Biodiversity

COP- Conference of Parties

DNA- Deoxyribo Nucleic Acid

DSI- Digital Sequence Information

HGP- Human Genome project

iGEM- International Genetically Engineered Machine

ITPGRFA- International Treaty on Plant Genetic Resource for Food and Agriculture

LMO- Living Modified Organisms

MEA- Multilateral Environmental agreement

SBI- Subsidiary Body on Implementation

SBSTTA- Subsidiary Body on Scientific, Technical and Technological Advice

SPS- Sanitary and Phytosanitary measures

TRIPS- Trade Related Aspects of Intellectual Property Rights

UPoV- Union for Protection of new Varieties of Plants

WTO- World Trade Organization

1. Introduction

Synthetic biology is a new area of research that combines biology with different fields i.e. mathematics, chemistry, computer science, and engineering to create, modify, and design biological components with new functions(Wang & Zhang, 2019).

The idea of synthetic biology was used in the 1980s within the works of literature to describe bacteria produced by genetic engineering. The synthesis of non-natural molecules that function in living things was begun in the early 2000s (Del Vecchio *et al*., 2018). These days, synthetic biology is portrayed by two principal lines of research. One is making and designing new biological parts and the other is assembling said parts into systems of increasing complexity (Decoene *et al*., 2018).

In 2014, the CBD established a technical group of experts called AHTEG in the field of synthetic biology. The Ad Hoc Technical expert group set an operational definition of synthetic biology: "Synthetic biology is a further development and new dimension of modern biotechnology that combines science, technology, and engineering to facilitate and accelerate the understanding, design, redesign, manufacture, and/or modification of genetic materials, living organisms and biological systems" (Scott, 2015).

1.1 Approaches to Synthetic Biology

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

1. "Biobricks" construction

Biobrick is a prefabricated, standardized, and modular DNA sequence that codes for certain functions. The development of standardized biological parts is popularly known as the legoization of biology. Standard biological parts can be freely combined with living cells to create new biological systems and devices that work as expected (Schmidt & Pei, 2011).

2. Synthetic metabolic pathway engineering

Metabolic engineering refers to the altering of several interacting genes or the introduction of new metabolic pathways within a cell or microorganism to direct the production of a specific substance, including the synthesis of natural products (pharmaceutical ingredients, flavors,

fragrances, oils, etc.) as well as high-value chemicals, plastics and fuels (Keasling, 2010). This process includes the design or redesign of a metabolic pathway by introducing several genes to an organism. Example applications include microbial (bio-factory) production of industrial chemicals, such as pharmaceuticals and biofuels, or microbial degradation of environmental pollutants (Pei *et al*., 2011).

3. Whole genome synthesis

Synthetic genomics is the process of creating a gene or full genome for which the complete DNA sequence is known by assembling synthetic (chemically produced) DNA strands (oligonucleotides). Researchers have used existing genomic sequence information to construct whole-length genomes from scratch. In 2002 researchers synthesized the 7,741 base poliovirus from the published sequence of the genome, producing the first synthetic virus constructed from DNA sequences.

In 2005 scientists synthesized the virus responsible for the 1918-19 flu pandemic. In 2008, scientists 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).

Genome-level engineering has two strategies: top down and bottom up.

- Top-down genome-engineering is a method of reducing genomes by removing unnecessary cellular genes to learn about genome architecture and improve its characteristics (Leprince *et al*., 2012).
- Bottom-up genome-engineering aims to build functional genomes from fragments of synthesized DNA; it is also referred to as "synthetic genomics" (Konig *et al*., 2013).

4. Proto-cell engineering

Researchers seeking to create a protocell are driven to design for less complexity at the cellular rather than genome level. "Protocells" are described as "models of artificial cells that have some characteristics of living systems but are not yet fully alive" (Schmidt, 2012).

5. XenoBiology

Xenobiology (also known as chemical synthetic biology) is the study of unusual life forms, based on biochemistry that is not naturally found (Pauwels *et al.*, 2012; Pei *et al.*, 2011). Xenobiology aims to alter the "biochemical building blocks of life," such as by modifying

genetic information to produce xenonucleic acids (XNA) or by producing novel proteins(Joyce, 2012).

One approach to producing XNA is to modify the nucleotide bases of DNA beyond A, G, C, and T, incorporating newly synthesized nucleotides into DNA molecules (Joyce, 2012; Pinheiro & Holliger, 2012; Sutherland *et al.,* 2014*).*

The second approach to XNA is replacing the "backbone" that the bases connect. That means information is stored via peptide nucleic acids (PNA), glycerol nucleic acids (GNA), and flexible nucleic acids (FNA) instead of deoxyribonucleic acid (DNA). The third approach involves modifying the nucleotides' pyrophosphate leaving group(Pinheiro & Holliger, 2012).

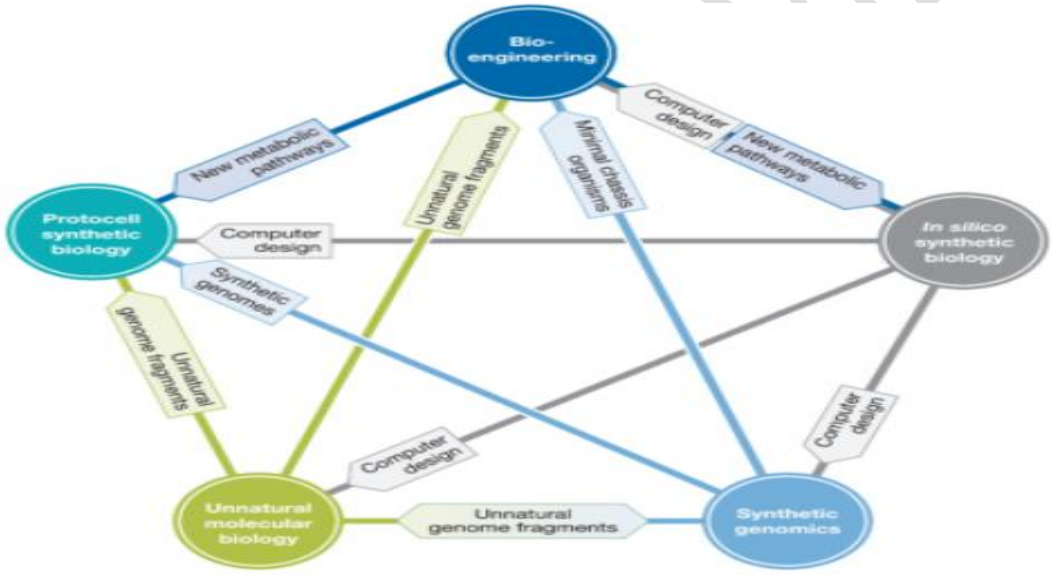

Fig 1. Schematic approaches of synthetic biology (Murphy *et al*., 2020)

1.2 Application of synthetic Biology

Synthetic biology is still an emerging field but there are growing numbers of applications in the pharmaceutical, chemical, agricultural, and energy sectors. Some of the products of synthetic biology are;

Production of Biofuel:

Synthetic biologists aim to improve the speed and efficiency of converting biomass into advanced, second or third-generation biofuels with cleaner and more favorable energy-usage profiles. This challenge may be met by creating "super-fermenting" yeast and bacteria through

synthetic biology. These organisms have the potential to boost the power and potential of current industrially used microorganisms by means of new or altered genes (Savage *et al*., 2008). Biofuels produced by engineered algae can be used as a sustainable alternative to fossil fuels, as they can be farmed without using arable land. As photosynthetic organisms, algae also remove CO_2 from the air, reducing it into energy-rich hydrocarbons(Georgianna & Mayfield, 2012).

Pharmaceutical products:

A notable example is the engineering of yeast cells that synthesize artemisinin, a drug used to treat malaria. Artemisinin is a naturally occurring chemical derived from the plant artemesia, or sweet wormwood. It is an effective malaria treatment but is difficult to obtain due to limitations on plant yield and high production costs. American scientists first reported the engineering of yeast to produce the precursor of artemisinin in 2006, which could then be purified, transportedand chemically converted into the full drug (Ro *et al*., 2006). This process has since been enhanced and now production of commercial semisynthetic artemisinin is underway by pharmaceutical company Sanofi (Paddon & Keasling, 2014), which may provide a model for the production of other pharmaceutical agents by synthetic biology.

Biosensor production:

There are projects underway to produce biosensors for polluted water for example *(*Rajakovic *et al.*, 2007). It is also possible to develop organisms that can process waste and purify water (and therefore restore damaged sites) by removing contaminants such as heavy metals and pesticides. One group of scientists (Kane *et al.*, 2016) recently developed *E.coli* able to degrade methylmercury, a toxic metal that can accumulate up the food chain. Synthetic biology has for some time been hailed as a potent contributor to food security, by developing new crop varieties that are resistant to pests or that have enhanced nutritional value.

1.3 Risks of Synthetic Biology

The risks created by the development of synthetic biology are of three types: biosafety, biosecurity and bioethics.

1.3.1 Biosafety concerns

The classification of biosafety risks is based on microorganisms' ability to cause disease for humans, animals, and plants regardless of severity (Kelle, 2009).

Biosafety risks associated with dual-use biotechnology have also been attracted by the rapid development of synthetic biology. Now a day insufficient work has been conducted to assess risks related to synthetic biology (Wikmark *et al.*, 2016).

According to (Hewett *et al.*, 2016) synthetic biology has risks to human health and pollution of the environment. The health-related risks include allergic problems, antibiotic resistance genes, carcinogens, and pathogenicity may increase; environmental risks include changes in the environment, competition with a native species, horizontal gene transfer, and pathogenicity.

Synthetic biology poses a biosafety concern for the intentional and unintentional release of synthetic organisms into the environment during the research and development process., although it has been argued that there is no risk owing to the vulnerability of synthetic organisms to displacement by native organisms (de Lorenzo, 2010).

Horizontal gene transfer is the main concerning issue related to moving synthetic biology beyond laboratory settings into real-world applications and it may have occurred when Synthetic DNA circuits consist of mobilized genes or sequences during conjugation or transduction (Nielsen *et al.*, 2007).

1.3.2. Biosecurity concerns

There is concern about the potential misapplication of synthetic biology for hostile uses. The rapid and inexpensive construction of long strands of synthetic DNA enables the production of known pathogens in the laboratory. These days, bioterrorism activity via the dual use of synthetic biology is the main biosecurity risk (Nordmann, 2010).

A major concern about synthetic biology is that in the wrong hands it could be used to intentionally create harmful organisms for bioterrorism. Recent examples of virus reconstruction using traditional recombinant DNA techniques fuel these concerns. These examples include the laboratory creation of infectious polio virus, the mycoplasma genome, and the 1918 strain of influenza virus (Kodumal *et al.*, 2004).

Highly pathogenic bacteria and viruses can be easily synthesized by taking those organisms' genetic sequences freely from websites such as Gene Bank, EMBL, and DDBJ; meanwhile, various viral, prokaryotic, and eukaryotic genomes can be synthesized at low prices using commercial services (Wang & Zhang, 2019).

In 2017, it was reported that synthesized horsepox virus was successfully constructed from overlapping DNA fragments ordered through the mail. The horsebox virus has a close evolutionary relationship with the variola virus (Medaglia *et al.*, 2015). The above activities have raised concerns among many virus experts, who have stated the need to strengthen the dual-use research supervision of biology, especially for research conducted in the private sector.

1.3.3 Ethical concerns with synthetic biology

Synthetic biology raises ethical issues around harms, benefits and risks. (Anderson *et al*., 2012) say: The ability to create synthetic organisms, combined with our inability to control them with solid guarantees, raises the need to consider the ethical implications. Synthetic biology aims to create living organisms from scratch and therefore challenges ideas about what is natural (Calvert, 2010). It may reduce how much people value what are now precious natural resources, and reduce support for conservation efforts in the expectation that extinct species can be brought back to life. A report entitled ‘‘The Ethics of Synthetic Biology and Emerging Technologies” was released to the public in 2010. In the report, experts concluded that the research at this stage still relied on an existing natural host, rather than creating life from inorganic chemicals alone. Complete human-made life remains only a remote possibility even in the foreseeable future.

In June 2016, a group of leading synthetic biologists announced that they will launch a Human Genome Project-Write (HGP-Write) federation, which will develop the relevant synthetic-biology technology required to chemically synthesize the human genome (Boeke *et al*., 2016). The misuse of outcomes of the HGP-Write project may increase public fear of technology. Prenatal genetic testing and selective abortions have led to concerns in many countries regarding unintended consequences of the HGP-Write project. While this may have some use, such a definition is unlikely to allay deeper concerns about the blurring of the boundary between the synthetic and the natural (Balmer and Martin, 2008), especially as machine learning is starting to rival world-class human game players.

2. International law on synthetic biology

2.1 Cartagena protocol on biosafety

The development of Biotechnology in the 1970s was accompanied by both excitement and concerns about the potential risks. As a result of the latter, the scientific community recommended that certain types of laboratory experiments be "voluntarily deferred" until a global scientific meeting could be held to examine scientific progress, identify potential risks, and determine the mechanism to manage them (Berg *et al.*, 1974). In 1975 more than 140 scientists attended a conference on recombinant DNA molecules at the Asilomar. Those scientists came from different institutions (Berg and Singer, 1995; Berg, 2008).

Recombinant DNA and associated "new" technologies remain the focus of regulatory policy debates in the twenty-first century, and there have been calls for a second Asilomar for "synthetic biology" (Endy, 2005). The 1992 earth summit of Rio De Janeiro has one significant outcome related to environmental protection called the Convention on Biological Diversity (CBD).

The main objective of CBD (Article 1):

i. The conservation of biodiversity;
ii. The sustainable use of the components of biodiversity;
iii. The fair and equitable sharing of the benefits arising from the utilization of genetic resources, including by appropriate access to genetic resources and by appropriate transfer of relevant technologies, taking into account all rights over those resources and to technologies, and by appropriate funding.

The Convention on Biological Diversity (CBD), Article 19(3), provided governments the mandate to consider the need for a protocol on biosafety to address the risks of genetic engineering. Negotiations on the CBD began in 1995 (COP2; Decision I/9) and the first subsidiary agreement to the CBD was adopted in 2000. This is the Cartagena Protocol on Biosafety to the CBD ("Cartagena Protocol") (Biosafety, 2005).

The Cartagena Protocol Entered into force on 11 September 2003 in 172 Parties and the Governing body is the Conference of the Parties serving as the meeting of the Parties (COP-MOP). The protocol lays out the guidelines for the safe handling, use, and transfer of living modified organisms (Keiper and Atanassova, 2020).

2.1.1 Objective of the protocol

The objective of Cartagena protocol stated in article 1 as:

"In accordance with the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development, the objective of this Protocol is to contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of living modified organisms resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, and specifically focusing on transboundary movements".

The objective of the Cartagena Protocol sets out the aim of the Protocol and has taken cognizance of the precautionary approach enshrined in Principle 15 of the Rio Declaration on Environment and Development. The Principle provides that:

"*Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation*."

The Cartagena Protocol is essentially a multilateral environmental agreement (MEA) to regulate environmental issues related to the intentional movement of LMOs. However, the Cartagena Protocol also deals with trade-related issues and includes the safe transfer of LMOs between parties. The legal effect of the objective is such that where a State signs the Protocol and becomes a Party, the State should strive to conform to the Objective of the Cartagena Protocol in the ratification process by ensuring that the enacted national law contributes to an adequate level of protection (Heinrich, 2002).

2.1.2 Definition of terms in CBD and Cartagena protocol

To determine whether the organisms, components, and products of synthetic biology are covered by the Cartagena Protocol on Biosafety, it is important to examine further some of the definitions under both the Protocol and its parent treaty, the CBD.

According to CBD article 2 terms are defined as follows:

"Biotechnology" means any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use. Many of the examples of organisms developed though synthetic biology can thus be considered as "living modified organisms resulting from biotechnology" as defined by the CBD.

"Genetic material" means any material of plant, animal, microbial or other origin, containing functional units of heredity.

"Genetic resource" means genetic material of actual or potential value.

Article 3 of Cartagena protocol – Use of terms (definitions)

*"**Living modified organism**" means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology.* A living modified organism is thus defined in the Protocol to include only those living organisms that;

- contain novel combinations of genetic material; and
- have been produced using the techniques of modern biotechnology (paragraph 208, An Explanatory Guide to the Cartagena Protocol on Biosafety (2003)).

A novel combination may be regarded as a combination that was not previously known to exist at the time it was first produced. Based on the Protocol's term usage "genetic material" (paragraphs 198–201), the Protocol's references suggested that "novel combination of genetic material" refers to a novel combination of nucleic acid containing functional units of heredity(paragraph 209,explanatory guide of Cartagena protocol ,2003).

*"**Living organism**" means any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids.* In the explanatory guide of Cartagena protocol, the virus, viroids and sterile organisms are defined as entities which cannot actively replicate genetic material or reproduce through sexual reproduction (paragraph 204 and 205).

The term LMO does not include naked DNA or plasmids. However, where a new combination of genetic material is introduced through the use of naked DNA or plasmids, the resultant organism qualifies as an LMO. The definition of an explanatory guide also covers a living organism in which a plasmid created by modern biotechnology and that contains a novel combination of genetic material is present, even where the plasmid is not integrated into the chromosomes of that organism (paragraphs 206 and 207, Explanatory Guide to Cartagena Protocol on Biosafety,2003).

*"**Modern biotechnology**" means the application of:*

a. In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or

b. Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.

The Protocol defines LMO according to whether the organism has a novel combination of genetic material combined with "modern biotechnology." Additionally, even if the novel combination of genes obtained through biotechnology is later transferred to an organism by traditional means, the resulting organism still qualifies as an LMO under the Protocol (paragraph 214, Explanatory Guide).

2.1.3 Transboundary Movement

The Primary focus of the Cartagena Protocol is the regulation of trans boundary movement of LMOs (Mackenzie *et al.*, 2003). However, its scope extends to all kinds of LMOs, including plants, food, pharmaceuticals, animals, insects, trees, for industrial use, etc.(Lim, 2007)

Article 3 (k) of the Cartagena Protocol defines Transboundary Movement as:

"…*the movement of a living modified organism from one Party to another Party, save that for the purposes of Articles 17 and 24 trans boundary movement extends to movement between Parties and non-Parties*".

A State that has signed/acceded or ratified the Protocol is a Party to the Protocol whereas a non-party is a State that is not a Party to the Treaty. This clearly means that what is to be regulated is the movement of LMOs between two Parties.

Two types of transboundary movements can be envisaged when considering synthetic biology: unintended and intended. Some applications of synthetic biology focus on particular geographies, contained within country borders. This is the case for applications against invasive species that intend to suppress those species locally but are not intended to have such effect on a global scale. If those applications were to be moved across borders, it would be an unintended or illegal transboundary movement. This could happen through natural dispersal of modified individuals, or through human transport (intentional or unintentional)(Redford *et al.*, 2019).

For unintended transboundary movement, there are existing governance frameworks. Under Article 17, the Cartagena Protocol requires countries to notify other countries that might be affected by an unintentional transboundary movement that may have an adverse effect on biodiversity. The Cartagena Protocol requires states from whose territory organisms are intentionally moved across borders to obtain advance informed agreement from the importing state. However, this provision was developed in the context of transboundary import and export, and it is not clear how it applies to intended or anticipated spread of modifications across borders (Emerson *et al.*, 2017).

2.1.4 Advance informed agreement (AIA)

The Protocol has a special focus on transboundary movements. The procedure by which transboundary movements of LMOs are regulated is known as the advance informed agreement (AIA) procedure which involves a few steps. If a LMO is to be exported, the exporting party notifies or requires its exporters to notify the importing party. The notification must include at least the information required (Information Required in Notifications under Articles 8, 10, and 13) of the Protocol. The notification is then acknowledged by the Party of import. If the importer follows its own domestic regulations, this decision must be consistent with the Protocol, or the procedure outlined in the Protocol may be followed (Lim, 2007).

The decision by the Party of import is based on risk assessment and precaution, and the Party of import may take into account socio-economic considerations when making its decision. A Party is obliged to consult its public in the decision-making process and must make the results of such decisions available to the public. A Party may make the following decisions: unconditional approval, approval with conditions, prohibition of the import, request for additional relevant information, or extension of the time period for making a decision.

According to AIA procedure, the Party of import must acknowledge receipt of notification within 90 days and has 270 days from the time it receives a notification to make its decision on the transboundary movement (Funtowicz and Strand, 2007).

2.2 Synthetic biology, CBD, and Cartagena protocol

Global legal framework addressing conservation, sustainable use, and sharing of benefits of biodiversity. Each party (Countries that have signed onto the Convention) is responsible for managing the risks associated with living modified organisms (LMOs) that would have a negative impact on biological diversity [article 8(g)]. According to Article 14 of the CBD, parties are obliged to conduct environmental impact assessments for avoiding or minimizing impacts on biological diversity. In addition to the Cartagena protocol, the CBD contains additional frameworks/requirements related to access and benefit-sharing of genetic resources (i.e., Nagoya Protocol) (Lai *et al.*, 2019).

To date, the CBD has its governing body, the COP, which held fourteen meetings and the 15th assembly of the COP (COP15) can be held in China in May 2022. The subsidiary bodies, the Subsidiary Body for Scientific, Technical, and Technological Advice (SBSTTA) and the Subsidiary Body for Implementation (SBI) of CBD aid the paintings of the COP. Keiper and Atanassova (2020b) count on SBSTTA24 will cope with the request of COP14 to do not forget the consequences of an application of labor that entails submissions of records on a sequence of artificial biology topics

As such, synthetic biology has been mentioned under the CBD considering that 2010. According to Decision X/13, Parties, other governments, and relevant organizations should take precaution when releasing synthetic life, cells, and genomes into the environment (Ching, 2017).

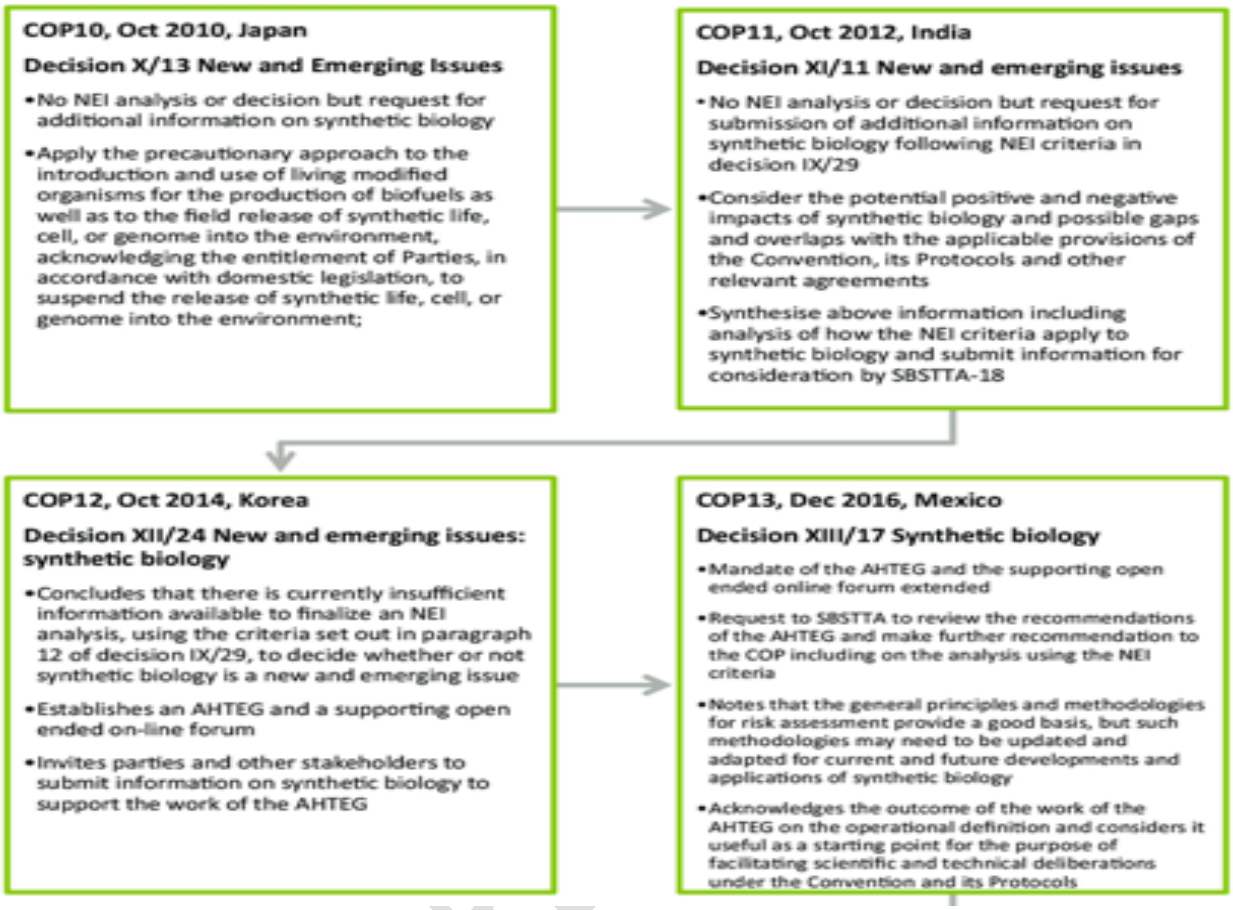

Figure 2 : Cartagena protocol

(Keiper and Atanassova, 2020)

At COP 13 in December 2016, Parties to the CBD considered the SBSTTA report and negotiated a new decision on synthetic biology (Decision XIII/17) which, among other things, extended the mandate of the current AHTEG with new terms of reference (see the annex).

The COP 14 was held in Egypt and in decision IX/29, the parties recognize that synthetic biology should be analyzed against NEI in order to determine whether it is in line with NEI. According to CBD technical series No.82, living organisms resulted from synthetic biology are categorized under the definition of "living modified organisms" of the Cartagena protocol.

Article 5 of the Cartagena protocol states that there are some limited exemptions of some living modified organisms from some provisions. The Protocol does not apply to the transboundary movement of LMOs which are pharmaceuticals for humans that are addressed by other relevant international agreements. Live virus vaccines are examples of LMOs produced by synthetic

biology which are used as pharmaceuticals for humans. However, as none of the organisms currently produced through synthetic biology that are intended to be used as pharmaceuticals for humans are directly addressed by other relevant international agreements or organizations, they therefore would arguably fall under the Cartagena Protocol's scope (Secretariat of the Convention on Biological Diversity, 2015).

The organisms used for synthetic biology, such as artemisinin, are not pharmaceuticals themselves. Instead, they are used as "biofactories" for the production of pharmaceuticals but they are still LMOs produced by synthetic biology and would therefore be covered by the Cartagena Protocol (Secretariat of the Convention on Biological Diversity, 2015).

3. Other international treaties relevant to synthetic biology

3.1 Treaties that address specific uses

3.1.1 Biological Weapon Convention (BWC)

Westing (1984) claims that a multinational disarmament treaty was built upon the Geneva Protocol of 1925, to prohibit biological and chemical weapons production, but not their use (Westing, 1984). The growth of bioweapons confronted the international community to produce the biological weapon Convention (BWC) in 1972(Nirmal, 2011).

According to BWC, States Parties to the Biological Weapons Convention undertook never in any circumstances to develop, produce, or accumulate:

- Microbial agents, or toxins, irrespective of their origin or methods of production, whose types or quantities are not justified for prophylactic or protective purposes;
- The use of such agents or toxins in hostile purposes or in armed conflict, whether in weapons, equipment, or delivery systems (Article 1 BWC, 1972).

3.1.2 Sanitary and Phytosanitary measures (SPS agreement)

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

According to secretariats of CBD, Some applications of synthetic biology could be considered as causing risks to animal or plant life or health arising from the entry, establishment or spread of pests, diseases, disease-carrying organisms or disease causing organisms; or as risks to human or animal life or health arising from additives, contaminants, toxins or disease-causing organisms in foods, beverages or feedstuffs (Secretariat of the Convention on Biological Diversity, 2015).

WTO members have the right to take sanitary and phytosanitary measures that are necessary for the protection of human, animal or plant life or health, even if these measures result in trade restrictions. However, these measures have to be consistent with the provisions of the SPS Agreement (Article 2, paragraph 1 SPS Agreement). Requirements include, for example, that the measures must be based on scientific principles, must not be discriminatory in their effect on other WTO members' exports, and must not be more trade-restrictive than is necessary to achieve the desired level of sanitary or phytosanitary protection (Articles 2, 3 and 5 SPS Agreement).

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

3.2 Treaties that address access and benefit-sharing

Beginning in 1992, the CBD attempted to address the concerns through its third major goal: to promote the fair and equitable sharing of the benefits arising from genetic resources (Coughlin Jr, 1993). The Cartagena Protocol added to this broad framework with provisions for information sharing and a Biosafety Clearing- House. It was not until 2010 that the international community earnestly addressed the CBD and Cartagena Protocol's shortcomings through the Nagoya Protocol (Buechle, 2001).

3.2.1 Nagoya Protocol

The Nagoya Protocol addresses the fair and equitable sharing of benefits derived from the sustainable use of genetic resources so as to conserve and protect biodiversity.It is Adopted in 2010 and entered into force in 2014 by 105 parties (Lai *et al.*, 2019).

The Protocol aimed to fulfill the CBD's third goal through the appropriate access to genetic resources and by the appropriate transfer of relevant technologies. It includes a provision on financial mechanisms to help developing countries with capacity-building and development requirements to implement the protocol(Rourke *et al.*, 2020).

As part of its Nagoya Protocol work, the CBD secretariat commissioned a report in 2017 that examined the implications of digital sequence information. Genetic resources can be used in synthetic biology, as well as in other nonscientific fields, to provide owners of the resources with new opportunities for nonmonetary and monetary benefit sharing but noted the risk that DSI

would undermine existing approaches to benefit-sharing by avoiding the need for access to genetic resources themselves(Laird and Wynberg, 2018).

The CBD and Nagoya Protocol contemplate regulation of the physical transfer of tangible genetic or biological material from a provider country to a user, pursuant to an ABS agreement. New technologies emerging from synthetic biology fundamentally change that paradigm, however. The genome of a particular species may now be sequenced within a provider country and that information may be transferred digitally to a company or research entity for downloading to a DNA synthesizer. As a result, synthetic biology technologies beg the question of whether ABS requirements should apply to the use of digital sequence information from genetic resources (Manheim, B.S., 2016).

3.3 treaties that address intellectual property right

The Convention on Biological Diversity aims for fair and equitable sharing of benefits arising out of the utilization of genetic resources (Lehman, 2008). From here the need to find a mechanism that works like a link between the Convention and intellectual property rights in order to ensure the transfer of knowledge.

The intellectual property rights in patents go hand-in-hand with genetic resources and the distribution of benefits, but patents can also hinder new technologies created through synthetic biology. The eternal dispute between those arguing that patents impede access to genetic resources on the one hand and those who believe that patents spur innovation in the field of new technologies on the other was presented here (Andermariam, 2007).

3.3.1 Trade Related Aspects of Intellectual Property Rights (TRIPS)

A comprehensive multilateral agreement on intellectual property, the WTO Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) went into effect on 1 January 1995.The purpose of TRIPS is to protect and enforce intellectual property rights, to contribute to technological innovation, and to transfer and disseminate technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations (article 7, TRIPS).

TRIPS article 27 outlines exclusions from patentability of diagnostic, therapeutic and surgical methods for treating plants and animals, as well as biological processes for growth and

production of plants or animals that are not biological and microbiological processes (paragraph 3 of TRIPS).

In certain cases, synthetic biology techniques could fall under the subject matter exclusions outlined in Article 27, paragraphs 2 & 3 of the TRIPS Agreement and hence would be excluded from patentability by some WTO members (Secretariat of the Convention on Biological Diversity, 2015). Paragraph 2 of Article 27 allows WTO members to provide this exclusion if it is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health, or to avoid serious prejudice to the environment. Several synthetic biology applications may meet these criteria in some countries, which may lead to their exclusion from patentability.

According to the TRIPS Agreement, each member has to provide certain standards of protection for intellectual property, including copyright and related rights, trademarks, and patents, which include the protection of new varieties of plants, among others. TRIPS identifies the subject matter to be protected, the rights to be conferred, and exceptions to those rights, as well as the minimum length of time for which this protection is to apply. Synthetic biology products, including components, organisms, and products, patents are most relevant, but copyright and trademarks have also been discussed in the literature(Torrance, 2010).

4. Gaps in the current regulatory framework

According to secretariats of CBD, general principles of international law and the rules of state have the duty to avoid transboundary harm and the need to conduct an environmental impact assessment (EIA). It may provide some guidance relevant to addressing potential negative impacts resulting from the application of synthetic biology techniques. But this would still form an incomplete basis to address all potential negative impacts (Secretariat of the Convention on Biological Diversity, 2015).

The synthetic biology technique may create components, organisms and products that are not living modified organisms, which may present a potential gap. While the products of some synthetic biology techniques, such as genome-level engineering, are expected to mostly produce living cells, it is less clear for other techniques.

Microorganisms resulting from synthetic metabolic pathway engineering produce molecules for use as pharmaceuticals, fuel, and other commercial uses. If these molecules are not living (as is the case for many of them), they may not be living modified organisms. Remaining questions include whether "naked" DNA, plasmids, and protocells would constitute living modified organisms. It would be a matter of interpretation whether products of xenobiology as organisms using different biochemical building blocks would be considered "living."

The CBD and its Protocols provide fairly comprehensive coverage but there are still gaps remaining. Work needs to continue in these fora to fully articulate to what extent they apply to synthetic biology, and how implementation should proceed. In particular, even though the requirements of the Cartagena Protocol apply to most, if not all, organisms resulting from current synthetic biology techniques, it may still be necessary, for example, to identify elements of risk assessment methodologies that would be specific for living organisms developed through synthetic biology in order to ensure the effective application of its risk assessment provisions (Secretariat of the Convention on Biological Diversity, 2015).

Many synthetic biology processes and transactions fall outside the scope of the Cartagena Protocol. First, the Cartagena Protocol only applies to physical transfer; it does not apply to the virtual (digital) transfer of LMO genetic material. Second, the protocol covers whole living organisms and cannot regulate ready-to-assemble constituent genetic parts. Finally, the Cartagena Protocol has a limited scope and cannot apply to research, creation and synthesis of biological parts, or the end-use of the products (Keiper and Atanassova, 2020).

The international community could list and ban the most dangerous synthetic biology products (i.e., the most likely to be used as bioweapons), but this would not be an easy task. While synthetic biology parts and processes may become weaponized in the wrong hands, they are not inherently "weapons" and would be difficult to classify. Further, Article IV directs parties to implement the BWC's objectives domestically. There is no international consensus to guide parties in creating domestic regulations. A new international governance scheme for synthetic biology must address the shortcomings of both the BWC and the CBD, discussed above.

Even though the BWC addresses general biosecurity concerns, the broad framework does not address problems specific to synthetic biology. First, the BWC — and perhaps any treaty designed solely to lessen biosecurity concerns — cannot account for synthetic biology's dual-use dilemma. The heart of synthetic biology is legitimate research used to bring positive societal advancements, but ill-willed actors may use its achievements for malicious purposes. The issue has been discussed explicitly under the Biological Weapons Convention (Tanimura, 2016).

5. Principles for a Holistic Regulatory Approach to Synthetic Biology

5.1 Potential adverse effects of synthetic biology

According to AHTEG on synthetic biology, non-exhaustive effects are grouped based on their impact on the three objectives of CBD (AHTEG, 2015):

Objective 1 of CBD: **Impacts on Conservation of biological diversity**

- Engineered fitness advantage may lead to invasiveness
- Loss of biodiversity due to increased gene flow
- Increased pathogenic potential
- Increased levels of toxic substances, which may be disruptive to the soil, food webs, and pollinators
- Negative effects on non-target organisms, such as pollinators
- Changes in organisms on the level of basic metabolic pathways, such as altered photosynthesis pathways, carbohydrate metabolism, or nitrogen fixation, may lead to changes in agricultural practice and land use
- Applications (such as gene drive systems) that alter or replace natural populations may adversely affect ecosystems

Objective 2 of CBD: **Impacts on Sustainable use of biological diversity**

- Increased demand for biomass crops, as well as changes in patterns of extraction of biomass, minerals, and other sources of energy, may lead to changes in land use
- The replacement of natural products could impact agricultural practices in communities, thereby causing adverse effects on traditional crops, practices, and livelihoods.
- Gene flow may lead to adverse effects on agrobiodiversity

Objective 3 of CBD: **Equitable sharing of the benefits of biological diversity**

- Loss of market share and income by indigenous/local communities due to altered exploitation of genetic resources
- There is a change in the understanding of what constitutes a genetic resource and the implications thereof, such as the misuse of original DNA information sources; and if benefits are derived from the use of such DNA information without prior informed consent and mutually agreed with terms, the fair and equitable sharing of the benefits would not be possible

- Inappropriate access without benefit-sharing due to the use of sequenced data without material transfer agreements under the Nagoya Protocol
- Access and benefit-sharing in synthetic biology may differ between patent-driven and open-source approaches
- Indigenous peoples and local communities will not necessarily support or benefit from the utilization of genetic resources in synthetic biology

5.2 Challenges for risk assessment

Organisms could be created through synthetic biology that will fundamentally differ from naturally occurring organisms, making it impossible to conduct risk assessments based on a comparative principle, due to the lack of appropriate comparators.

Risk assessment may therefore be more challenging for synthetic biology, as the complexity of organisms increases, novel gene sequences are more significantly modified, and genetic components are assembled from a greater variety of sources. According to secretariats of CBD, principles, and methodologies that are currently applied to evaluate LMOs will raise specific challenges and limitations for future development of synthetic biology (Secretariat of the Convention on Biological Diversity, 2015).

Due to the complexity and novelty of the organisms developed through new technologies such as synthetic biology, the type and depth of information that may be required to assess their risks will likely differ from the information typically provided by developers for conducting risk assessments of LMOs(Eckenstorfer *et al.*, 2014).

Given the acknowledged challenges for risk assessment that could be posed by synthetic biology, the AHTEG on Risk Assessment and Risk Management, established under the Cartagena Protocol on Biosafety, discussed the issue in 2016. The AHTEG developed an outline of guidance on “Risk Assessment of LMOs developed through synthetic biology”, and the issue was discussed at the Eighth Conference of the Parties serving as the Meeting of the Parties (COP-MOP 8) to the Cartagena Protocol in December 2016.

The AHTEG agreed that broad and regular horizon scanning, monitoring, and assessing of the most recent technological developments are needed for reviewing new information regarding the

potential positive and potential negative impacts of synthetic biology in the COP 14 meeting held in Egypt in 2018(Decision XIV/19).

5.3 Principles for a regulatory approach

According to (Gómez-Tatay and Hernández-Andreu, 2019) the following are some principles that could apply in order to foster a holistic regulatory approach to synthetic biology;

Risk assessment

- In order to address the potential adverse effects of synthetic biology, risk assessment becomes necessary.
- This should be a pre-market case-specific assessment that considers direct, indirect, immediate and delayed impacts, and cumulative long-term effects.
- Risk assessment should also take into account risks to human health, and the need to protect public health and worker safety.
- Given that synthetic biology carries many scientific uncertainties, there should always be an acknowledgment of the gaps in scientific knowledge, potential unintentional effects, and consideration of uncertainties, including making these known to decision-makers.
- If any organism, product, or component of synthetic biology is approved, this should be a time-bound approval and reassessment required in case of new information arising.
- There should be mandatory regulations applicable to synthetic biology, so as to minimize the potential adverse effects.

Conclusion

Synthetic biology is still an emerging field and in the past decade, rapid growth has been made in synthetic biology, which has made significant contributions to basic life science research, human health, environmental protection, and economic growth. As synthetic biology becomes less expensive, easier to use, and more accessible, any unintentional misuse or deliberate abuse of dual-use synthetic biology will have serious consequences for the economy and security at international levels. The technological application and development of synthetic biology, however, are associated with unknown bio-risks, due to limitations in our understanding of life's code and the potential for unintended or intended uses of the technology.

In order to manage the issue of bio-risk concerns, there is a great need for legislative and regulatory constraints and oversight when one is working with synthetic biology technologies, especially when dual-use biotechnology is involved. To address ethics concerns, which in most cases have been caused by misunderstanding of the technology, a public dialog on synthetic biology held by scientists and social experts will be helpful.

Reference

Andermariam, S. (2007). The cleft-stick between antiretroviral drug patients and HIV/AIDS victims: an in-depth analysis of the WTO's TRIPS Article 31 bis Amendment proposal of 6 December 2005. *Intellectual Property Quarterly*, 414-466.

Anderson, G., & Oderkirk, J. (2005). Dementia Research and Care. Can Big Data help? Paris: OECD Publishing.

Anderson, J., Strelkowa, N., Stan, G.B., Douglas, T., Savulescu, J., Barahona, M. and Papachristodoulou, A. (2012). Engineering and ethical perspectives in synthetic biology: Rigorous, robust and predictable designs, public engagement and a modern ethical framework are vital to the continued success of synthetic biology. *EMBO reports*, **13**(7), pp.584-590.

Balmer, A. and Martin, P., P (2008) Synthetic biology: social and ethical challenges. Retrieved August 29, 2009, from. In University of Nottingham, Institute for Science.

Berg, P., Baltimore, D., Boyer, H.W., Cohen, S.N., Davis, R.W., Hogness, D.S., Nathans, D., Roblin, R., Watson, J.D., Weissman, S. and Zinder, N.D. (1974). Potential biohazards of recombinant DNA molecules. *Science*, **185**(4148), pp.303-303.

Berg, P. (2008) 'Asilomar 1975: DNA modification secured', *Nature*, 455(7211), pp. 290–291.

Berg, P. and Singer, M. F. (1995) 'The recombinant DNA controversy: twenty years later., Proceedings of the *National Academy of Sciences of the United States of America*, **92**(20), p. 9011.

BIOSAFETY, P. O. N. (2005) 'Convention on Biological Diversity', EUROPE (UNECE).

Boeke, J.D., Church, G., Hessel, A., Kelley, N.J., Arkin, A., Cai, Y., Carlson, R., Chakravarti, A., Cornish, V.W., Holt, L. and Isaacs, F.J., (2016). The genome project-write we need technology and an ethical framework for genome-scale engineering. *Science*, **353**(6295), pp.126-127.

Buechle, K. (2001) 'the great, global promise of genetically modified organisms: overcoming fear, misconceptions, and the Cartagena Protocol on Biosafety', *Ind. J. Global Legal Stud*., 9, p. 283.

Calvert, J. (2010) 'Synthetic biology: constructing nature?' *The Sociological Review*, **58**(1_suppl), pp. 95–112.

Calvert, J., (2012). Ownership and sharing in synthetic biology: A 'diverse ecology'of the open and the proprietary? *BioSocieties*, ***7***(2), pp.169-187.

Conde, C. A. (2012). Consecuencias de la biología sintética en los derechos de propiedad intelectual y acceso a los recursos genéticos y distribución de beneficios. *La propiedad Inmaterial.* , 16, pp. 281.

Ching, L. L. (2017) 'synthetic biology and relevant international law'.

Coughlin Jr, M. D. (1993) 'Using the Merck-INBio agreement to clarify the Convention on Biological Diversity', *Colum. J. Transnat'l L.*, 31, pp. 337.

De Lorenzo, V. (2010) 'Environmental biosafety in the age of synthetic biology: do we really need a radical new approach? Environmental fates of microorganisms bearing synthetic genomes could be predicted from previous data on traditionally engineered bacteria for in situ biore', BioEssays: *news and reviews in molecular, cellular and developmental biology*, **32**(11), pp. 926–931.

Decoene, T., De Paepe, B., Maertens, J., Coussement, P., Peters, G., De Maeseneire, S.L. and De Mey, M., (2018). Standardization in synthetic biology: an engineering discipline coming of age. *Critical reviews in biotechnology*, **38**(5), pp.647-656.

Del Vecchio, D., Qian, Y., Murray, R.M. and Sontag, E.D.(2018). Future systems and control research in synthetic biology. *Annual Reviews in Control*, 45, pp.5-17.

Eckenstorfer, M., Miklau, M. and Gaugitsch, H. (2014) New plant breeding techniques and risks associated with their application.

Emerson, C., James, S., Littler, K. and Randazzo, F., 2017. Principles for gene drive research. *Science*, **358**(6367), pp.1135-1136..

Endy, D. (2005) 'Foundations for engineering biology', *Nature*, **438**(7067), pp. 449–453.

.Funtowicz, S. and Strand, R. (2007) 'Models of science and policy', Biosafety first: Holistic approaches to risk and uncertainty in genetic engineering and genetically modified organisms, pp. 263–278.

Georgianna, D. R. and Mayfield, S. P. (2012) 'Exploiting diversity and synthetic biology for the production of algal biofuels', *Nature*, **488**(7411), pp. 329–335.

Gibson, D.G., Benders, G.A., Andrews-Pfannkoch, C., Denisova, E.A., Baden-Tillson, H., Zaveri, J., Stockwell, T.B., Brownley, A., Thomas, D.W., Algire, M.A. and Merryman,

C., (2008). Complete chemical synthesis, assembly, and cloning of a Mycoplasma genitalium genome. *science*, **319**(5867), pp.1215-1220.

Gómez-Tatay, L. and Hernández-Andreu, J. M. (2019) 'Biosafety and biosecurity in synthetic biology: a review', *Critical Reviews in Environmental Science and Technology*, **49**(17), pp. 1587–1621.

Heinrich, M. (2002) Handbook of the Convention on Biological Diversity, *Journal of Ethnopharmacology*. doi: 10.1016/s0378-8741(02)00043-0.

Hewett, J.P., Wolfe, A.K., Bergmann, R.A., Stelling, S.C. and Davis, K.L., (2016). Human health and environmental risks posed by synthetic biology R&D for energy applications: a literature analysis. *Applied Biosafety*, **21**(4), pp.177-184.

Joyce, G. F. (2012) 'Toward an alternative biology', *Science*, **336**(6079), pp. 307–308.

Kane, A.L., Al-Shayeb, B., Holec, P.V., Rajan, S., Le Mieux, N.E., Heinsch, S.C., Psarska, S., Aukema, K.G., Sarkar, C.A., Nater, E.A. and Gralnick, J.A.,(2016). Toward bioremediation of methylmercury using silica encapsulated Escherichia coli harboring the mer operon. *PloS one*, **11**(1), p.e0147036.

Keasling, J. D. (2010). 'Manufacturing molecules through metabolic engineering', *Science*, **330**(6009), pp. 1355–1358.

Keiper, F. and Atanassova, A. (2020). 'Regulation of synthetic biology: developments under the convention on biological diversity and its protocols', *Frontiers in Bioengineering and Biotechnology*, 8, p. 310.

Keiper, F. and Atanassova, A. (2020). 'Regulation of Synthetic Biology: Developments Under the Convention on Biological Diversity and Its Protocols', *Frontiers in Bioengineering and Biotechnology*, 8(April), pp. 1–20. doi: 10.3389/fbioe.2020.00310.

Kelle, A. (2009). 'Synthetic biology and biosecurity: from low levels of awareness to a comprehensive strategy', *EMBO reports*, **10**(S1), pp. S23–S27.

Kodumal, S.J., Patel, K.G., Reid, R., Menzella, H.G., Welch, M. and Santi, D.V., (2004). Total synthesis of long DNA sequences: synthesis of a contiguous 32-kb polyketide synthase gene cluster. *Proceedings of the National Academy of Sciences*, **101**(44), pp.15573-15578.

Konig, H., Frank, D., Heil, R. and Coenen, C.(2013). Synthetic genomics and synthetic biology applications between hopes and concerns. *Current genomics*, **14**(1), pp.11-24

Lai, H.E., Canavan, C., Cameron, L., Moore, S., Danchenko, M., Kuiken, T., Sekeyová, Z. and Freemont, P.S.(2019). Synthetic biology and the United Nations. *Trends in biotechnology*, **37**(11), pp.1146-1151.

Laird, S. and Wynberg, R. (2018). 'A fact-finding and scoping study on digital sequence information on genetic resources in the context of the Convention on Biological Diversity and the Nagoya Protocol', in Rio de Janeiro: Convention on Biological Diversity.

Lehman, M. (2008). Technology transfer under the Convention on Biological Diversity and the Role of Intellectual Property Rights. WIPO Life Sciences Symposium: Patent Landscaping and Transfer of Technology under Multilateral Environmental Agreements. Geneva: WIPO.

Leprince, A., van Passel, M. W. J. and dos Santos, V. A. P. M. (2012). 'Streamlining genomes: toward the generation of simplified and stabilized microbial systems', *Current opinion in biotechnology*, **23**(5), pp. 651–658.

Lim, L. (2007). 'Chapter 26 Cartagena Protocol on Biosafety', BIosafety First, pp. 2–18.

Mackenzie, R. (2003). An Explanatory Guide to the Cartagena Protocol on Biosafety, An Explanatory Guide to the Cartagena Protocol on Biosafety. doi: 10.2305/iucn.ch.2003.eplp.46.en.

Manheim, B.S.(2016). Regulation of synthetic biology under the Nagoya Protocol. Nature biotechnology, **34**(11), pp.1104-1105.

Medaglia, M.L.G., Moussatché, N., Nitsche, A., Dabrowski, P.W., Li, Y., Damon, I.K., Lucas, C.G., Arruda, L.B. and Damaso, C.R.(2015). Genomic analysis, phenotype, and virulence of the historical Brazilian smallpox vaccine strain IOC: implications for the origins and evolutionary relationships of vaccinia virus. *Journal of virology*, **89**(23), pp.11909-11925.

Mendel, G., & Marchant, G. E. (2014). The living regulatory challenges of synthetic biology. *Iowa Law Review*, 158.

Murphy, C., Deplazes, E., Cranfield, C.G. and Garcia, A., 2020. The role of structure and biophysical properties in the pleiotropic effects of statins. *International journal of molecular sciences*, **21**(22), p.8745.

Nielsen, K.M., Johnsen, P.J., Bensasson, D. and Daffonchio, D. (2007). Release and persistence of extracellular DNA in the environment.*Environmental biosafety research*, **6**(1-2), pp.37-53

Nirmal, B. C. (2011). 'Implementation of the Biological Weapons Convention and the Indian State Practice', *ISIL YB Int'l Human. & Refugee L*., 11, p. 107.

Nordmann, B. D. (2010). 'Issues in biosecurity and biosafety', *International Journal of Antimicrobial Agents*, 36, pp. S66–S69.

Paddon, C. J. and Keasling, J. D. (2014). 'Semi-synthetic artemisinin: a model for the use of synthetic biology in pharmaceutical development', *Nature Reviews Microbiology*, **12**(5), pp. 355–367.

Paris, K. (2001). 'The Expansion of the Biological Weapons Convention: The History and Problems of a Verification Regime', *Hous. J. Int'l L*., 24, p. 509.

Pauwels, K., Willemarck, N., Breyer, D. and Herman, P. (2012). Synthetic Biology: Latest developments, biosafety considerations and regulatory challenges. Scientific Institute of Public Health (Belgium).

Pei, L., Schmidt, M. and Wei, W. (2011). 'Synthetic biology: an emerging research field in China', *Biotechnology advances*, **29**(6), pp. 804–814.

Pinheiro, V. B. and Holliger, P. (2012). 'The XNA world: progress towards replication and evolution of synthetic genetic polymers', *Current opinion in chemical biology*, **16**(3–4), pp. 245–252.

Rajakovic, V., Aleksic, G., Radetic, M. and Rajakovic, L. (2007). Efficiency of oil removal from real wastewater with different sorbent materials. *Journal of hazardous materials*, **143**(1-2), pp.494-499.

Redford, K.H., (2019). Genetic frontiers for conservation (No. BOOK_B). Union internationale pour la conservation de la nature.

Ro, D.K., Paradise, E.M., Ouellet, M., Fisher, K.J., Newman, K.L., Ndungu, J.M., Ho, K.A., Eachus, R.A., Ham, T.S., Kirby, J. and Chang, M.C. (2006). Production of the antimalarial drug precursor artemisinic acid in engineered yeast. *Nature*, **440**(7086), pp.940-943

Rourke, M., Halabi, S., Burci, G.L. and Katz, R. (2020). The Nagoya Protocol and the legal structure of global biogenomic research. *Yale J. Int'l L*., 45, p.133.

Sanderson, J. (2017). Plants, people and practices: the nature and history of the UPOV Convention. Cambridge University Press.

Savage, D. F., Way, J. and Silver, P. A. (2008). 'Defossiling fuel: how synthetic biology can transform biofuel production. Citeseer.

Schmidt, M. (2012). Synthetic biology: industrial and environmental applications. John Wiley & Sons.

Schmidt, M., and Pei, L. (2011). 'Synthetic toxicology: where engineering meets biology and toxicology', *Toxicological Sciences*, **120**(suppl_1), pp. S204–S224.

Scott, D. (2015). 'Framing and responding to scientific uncertainties: biofuels and synthetic biology at the convention on biological diversity, *Jurimetrics*, 56, p. 245.

St. Laurent, A. M. (2004). Understanding Open Sources and Free Software Licensing. CA, USA: O'reilly Media Inc.

Sutherland, W.J., Aveling, R., Brooks, T.M., Clout, M., Dicks, L.V., Fellman, L., Fleishman, E., Gibbons, D.W., Keim, B., Lickorish, F. and Monk, K.A. (2014). A horizon scan of global conservation issues for 2014. *Trends in ecology & evolution*, **29**(1), pp.15-22.

Tanimura, E., Creating International Governance for Synthetic Biology: Identifying the Principles and Players.

Torrance, A. W. (2010). 'Synthesizing law for synthetic biology', *Minn. JL Sci. & Tech*., 11, p. 629.

Wacker, M.G. (2014). Nanotherapeutics—Product development along the "nanomaterial" discussion. *Journal of Pharmaceutical Sciences*, **103**(3), pp.777-784.

Wang, F. and Zhang, W. (2019). 'Synthetic biology: Recent progress, biosafety and biosecurity concerns, and possible solutions', *Journal of Biosafety and Biosecurity*, **1**(1), pp. 22–30. doi: 10.1016/j.jobb.2018.12.003.

Westing, A. H. (1984). 'Environmental warfare', *Envtl. L*., 15, p. 645.

Wikmark, O.G., Brautaset, T., Agapito-Tenfen, S.Z., Okoli, A.S., Myhr, A.I., Binimelis, R. and Ching, L.L. (2016). Synthetic biology–biosafety and contribution to addressing societal challenges.

Annex

TERMS OF REFERENCE FOR THE AD HOC TECHNICAL EXPERT GROUP ON SYNTHETIC BIOLOGY

1. Building on the previous work of the Online Forum and Ad Hoc Technical Expert Group, and drawing upon relevant information submitted by Parties, other Governments, relevant organizations and indigenous people s and local communities through paragraph 10 , as well as information made available through the online forum and by the Secretariat, the Ad Hoc Technical Expert Group on Synthetic Biology shall, in coordination with other bodies of the Convention and its Protocols:

(a) Review recent technological developments within the field of synthetic biology to assess if the developments could lead to impacts on biodiversity and the three objectives of the Convention, including unexpected and significant impacts;

(b) Identify any living organisms already developed or currently under research and development through techniques of synthetic biology which do not fall under the definition of living modified organisms under the Cartagena Protocol;

(c) Further analyze evidence of benefits and adverse effects of organisms, components, and products of synthetic biology vis à vis the three objectives of the Convention, and gather information on risk management measures, safe use, and best practices for safe handling of organisms, components and products of synthetic biology;

(d) In order to avoid or minimize any potential negative effects on the conservation and sustainable use of biodiversity, evaluate the availability of tools to detect and monitor the organisms, components, and products of synthetic biology;

(e) Provide, for consideration by the Subsidiary Body on Scientific, Technical and Technological Advice at a meeting held prior to the fourteenth meeting of the Conference of the Parties recommendations on the basis of its deliberations to facilitate future discussions and actions on synthetic biology under the Convention, as well as an analysis against the criteria set out in paragraph 12 of decision IX/29 to contribute to the completion of the assessment requested in paragraph 2 of decision XII/24 by the Subsidiary Body on Scientific, Technical and Technological Advice;

2. Subject to the availability of funds, the Ad Hoc Technical Expert Group shall meet at least once face to face prior to the fourteenth meeting of the Conference of the Parties and make use of online tools to facilitate its work, as appropriate.

Conference of parties	**Decisions related to synthetic biology**
COP10, Oct 2010, Japan Decision X/13 New and Emerging Issues	▪ No NEI analysis or decision but a request for additional information on synthetic biology. ▪ Apply the precautionary approach to the introduction and use of living modified organisms for the production of biofuels as well as to the field release of synthetic life, cell, or genome into the environment, acknowledging the entitlement of Parties, in accordance with domestic legislation, to suspend the release of synthetic life, cell, or genome into the environment
COP 11, Oct 2012, India Decision XI/11 New and emerging issues	▪ No NEI analysis or decision but a request for submission of additional information on synthetic biology following NEI criteria in decision IX/29 ▪ Consider the potential positive and negative impacts of synthetic biology and possible gaps and overlaps with the applicable provisions of the Convention, its Protocols and other relevant agreements ▪ Synthesize above information including analysis of how the NEI criteria apply to synthetic biology and submit information for consideration by SBSTTA-18

COP12, Oct 2014, Korea Decision XII/24 New and emerging issues: synthetic biology	▪ Concludes that there is currently insufficient information available to finalize an NEI analysis, using the criteria set out in paragraph 12 of decision IX/29, to decide whether or not synthetic biology is a new and emerging issue ▪ Establishes an AHTEG and a supporting open ended on-line forum ▪ Invites parties and other stakeholders to submit information on synthetic biology to support the work of the AHTEG
COP13,Dec 2016, Mexico Decision XIII/17 Synthetic biology	▪ The mandate of the AHTEG and the supporting open ended online forum extended ▪ Request to SBSTTA to review the recommendations of the AHTEG and make further recommendation to the COP including on the analysis using the NEI criteria ▪ Notes that the general principles and methodologies for risk assessment provide a good basis, but such methodologies may need to be updated and adapted for current and future developments and applications of synthetic biology ▪ Acknowledges the outcome of the work of the AHTEG on the operational definition and considers it useful as a starting point for the purpose of facilitating scientific and technical deliberations under the Convention and its Protocols
COP14, Nov 2018, Egypt Decision XIV/19 Synthetic biology	▪ Agrees that broad and regular horizon scanning, monitoring and assessing of the most recent technological developments is needed for reviewing new information regarding the potential positive and potential negative impacts of synthetic biology ▪ Recognizes the need to conduct an analysis of synthetic biology against the NEI criteria in decision IX/29, paragraph 12, in order to complete the analysis of whether synthetic biology meets the criteria for a NEI ▪ Mandate of the AHTEG and the supporting open ended online forum extended ▪ The Executive Secretary to update the Technical Series on Synthetic Biology and cooperation with other organizations

COP 15 is scheduled to be a meeting in Kunming, China, from 25 April-8 May 2022.	