Source: Macroscopic Solutions, LLC

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

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

2. CONVENTION ON BIOLOGICAL DIVERSITY

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

2.1. Principle of the Convention (Article 3)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.3.1. "Living modified organisms"

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

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

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

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

Source: Macroscopic Solutions, LLC

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

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

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

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

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

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

2.3.3. "Use and release of living modified organisms

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

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

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

Source: Macroscopic Solutions, LLC

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

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

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

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

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

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

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

3. CARTAGENA PROTOCOL ON BIOSAFETY

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

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

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

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