Third World Network submission of information on synthetic biology

1. How to address the relationship between synthetic biology and biological diversity

The relationship between synthetic biology and biological diversity should be addressed on the basis of the objectives of the Convention on Biological Diversity (CBD). These oblige Parties to ensure the conservation of biological diversity, the sustainable use of its components and equitable sharing of the benefits arising out of the utilization of genetic resources. Articles 7, 8, 13, 14 and 17 of the CBD appear to be particularly relevant in relation to synthetic biology.

In so far as organisms resulting from synthetic biology techniques meet the definition of living modified organisms (LMOs) under the Cartagena Protocol on Biosafety, then the provisions of the Cartagena Protocol and its Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress should be applied. These are inclusive of a precautionary approach, advanced informed agreement, risk assessment and risk management, socio-economic considerations, public participation, and liability and redress.

Drawing on the above, the relationship between synthetic biology and biological diversity could be addressed by ensuring that the direct and indirect risks to the conservation and sustainable use of biological diversity, of organisms, components or products derived from synthetic biology techniques, are assessed prior to any introduction to the environment or placing on the market, in a precautionary manner, taking also into account risks to human health and socio-economic considerations, especially with regard to the value of biological diversity to indigenous and local communities. Damage resulting from the organisms, components and products of synthetic biology techniques must also be addressed through a liability and redress regime.

In regard to access and benefit sharing (ABS), synthetic biology may potentiate misappropriation of genetic resources (i.e. biopiracy). This is because synthetic biology enables transfer of functional units of heredity in digital (or "virtual" form), and the subsequent synthesis and use of those units.

Since many ABS approaches are predicated on physical access to biodiversity, for example implementing obligations through a Material Transfer Agreement, digital transfer of synthesizable sequence data may evade rules as presently drafted or implemented.

To put it simply, if yesterday's biopirate hid seeds in his luggage, tomorrow's biopirate may upload data at her hotel, or carry it onto her flight on a USB stick.

For some small microorganisms, it is already possible to create entire living organisms wholly from sequence data. This can be accomplished in a very short period - a few days or less - once that sequence information becomes available (e.g. in an online database). Presumably, this ability will get faster and involve larger organisms over time.

A real world example of this occurring is described by Dormitzer, et al (Sci Transl Med 15 May 2013) where an H7N9 influenza strain isolated in China was synthesized in the US and cultured in a vaccine facility within days of the sequence being posted on an internet database. This virus appears to have been synthesized because US companies and authorities did not wish to wait to receive a physical sample of the virus from China. Notably, had the US entities waited a few days, a sample of the H7N9 strain would have been available to them under the Standard Material Transfer Agreement utilized by WHO's Pandemic Influenza Preparedness Framework (http://www.who.int/influenza/pip/en/).

In agriculture, the Diversity Seek program (http://www.divseek.org) is prompting similar concerns. Diversity Seek (Divseek) aims to place large new swathes of crop gene sequence data in new and sophisticated interoperating databases. The species of interest for Divseek include both those covered by ITPGRFA Annex 1 and others that are not covered by a specialized instrument, particularly crop wild relatives. Technologically, the point at which these gene sequences may be digitally accessed, synthesized, and practically used by plant breeders in crop varieties is close.

Notably, at least one Divseek principal has asserted her belief that by transferring sequence data digitally, access and benefit sharing rules might be avoided: "*Genotype information can move quickly and is not in fact subject to the same laws as a genetic resource itself*," Susan McCouch of Cornell University has asserted, adding "*Information alone can be critical. There are many many different sources of the same alleles. Most alleles in the world are already distributed on many continents and in many genetic backgrounds*." (See: McCouch S (2014). "The Importance of Data Sharing and Germplasm Movement", presentation at the Borlaug Global Rust Initiative Summit on Wheat for Food Security (conference), Ciudad Obregon, Mexico, 26 March.)

What applies for microorganisms and agricultural crops generally will also apply to digitally transferred and synthesized functional units of heredity of medicinal plants and other biodiversity.

In sum, synthetic biology presents challenges to fair and equitable benefit sharing because it enables evasion of ABS systems that are built a presumption of physical transfer of materials. Digital movement across borders and subsequent synthesis and use of functional units of heredity - and even entire organisms - will thus need to be addressed in order to prevent biopiracy facilitated by synthetic biology.

2. The similarities and differences between living modified organisms (as defined in the Cartagena Protocol) and organisms, components and products of synthetic biology techniques

The organisms, components and products of synthetic biology techniques are products of 'modern biotechnology' as defined under the Cartagena Protocol on Biosafety and the Codex Alimentarius Principles for the Risk Analysis of Foods Derived from Modern Biotechnology. Any organism modified using *in vitro* nucleic acid techniques should be considered a 'synthetically modified organism', whether or not there is a novel combination of genetic material. These techniques would include genome

editing technologies such as cisgenic, intragenic, reverse breeding, TALEN, meganucleases, ZFN and CRISPR/Cas.

In so far as organisms resulting from synthetic biology techniques meet the definition of LMOs under the Cartagena Protocol on Biosafety, then they are also LMOs. It should be pointed out however, that the Cartagena Protocol only addresses products thereof under its Article 20, Annex I and Annex III, so its scope is limited in relation to the components and products of synthetic biology.

As such, the organisms, components and products of synthetic biology techniques make up a broader category than 'living modified organisms' (LMOs) as defined under the Cartagena Protocol.

3. Adequacy of existing national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques

In so far as organisms resulting from synthetic biology techniques meet the definition of living modified organisms (LMOs) under the Cartagena Protocol, then they are also LMOs and should be regulated accordingly, including under the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress. The Cartagena Protocol however, only addresses products thereof under its Article 20, Annex I and Annex III, so its scope is limited in relation to components and products of synthetic biology.

As the organisms, components and products of synthetic biology techniques make up a broader category than LMOs as defined under the Protocol, there is an urgent need for their adequate regulation at national, regional and international levels, with a boarder definition of this application of modern biotechnology (as defined under the Cartagena Protocol and the Codex Alimentarius Principles for the Risk Analysis of Foods Derived from Modern Biotechnology), and explicitly including products of genome editing technologies.

Moreover, while the existing processes under the Cartagena Protocol and Codex Alimentarius largely (but not exclusively) focus on risk assessment, there is a lack of national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques that at the same time comprehensively include socio-economic impacts and the issue of liability and redress.

4. An operational definition of synthetic biology, comprising inclusion and exclusion criteria

<u>Proposed definition of synthetic biology</u>

Any activity utilizing synthetic nucleic acids or synthetic nucleic acid products.

<u>Proposed definition of synthetic nucleic acids (SNAs)</u>

Nucleic acid molecules that are chemically or by other means synthesized, including those that are chemically or otherwise modified, and molecules that result from the replication thereof.

Proposed definition of Synthetic Nucleic Acid Products (SNAPs)

Molecules wholly or partially resulting from synthetic nucleic acids.

Notes:

1. Inclusion and exclusion criteria are provided in the definition of SNAs and SNAPs.

2. While LMOs and organisms, components and products of synthetic biology may sometimes be distinguished from one another, entirely mutually exclusive definitions are not possible because the technologies are related and frequently used together.

3. Products of genome editing technologies are encompassed by the definition.

4. Synthetically replicated naturally occurring nucleic acids (e.g. viruses synthesized from sequence data) are included, whether or not they incorporate modifications.

5. Potential benefits and risks of organisms, components and products arising from synthetic biology techniques to the conservation and sustainable use of biodiversity and related human health and socioeconomic impacts relevant to the mandate of the Convention and its Protocols

There are potential risks to the conservation and sustainable use of biodiversity and related human health and socio-economic impacts posed by the organisms, components and products arising from synthetic biology techniques.

Among its risks, synthetic biology poses significant risks for the spread of pathogens and other microbial populations that can have deleterious effects on biodiversity and human health as well as socio-economic impacts.

For some small organisms, it is presently possible to generate, from genetic sequence data, synthetic living materials that wholly replicate the sequences of natural organisms and that optionally also incorporate synthetic modifications. This technology is well demonstrated for RNA viruses such as orthomyxoviruses (influenza), coronaviruses (SARS, MERS, etc.) and picornaviruses (polio, etc.) and is quite likely extensible to other small RNA virus families such as filoviruses (Ebola, Marburg, etc.).

For example, highly pathogenic stains of influenza virus, which can have devastating effects on a variety of avian and mammalian species, including humans, can be synthesized in a matter of only a few days following their initial isolation and sequencing, and placement of that sequence in an electronic database (as is the norm).

There are no geographic constraints, and few legal constraints, on such procedures, which enable the spread of plant and animal pathogens by synthetic biology. Such

spread of plant and animal diseases, which can leapfrog traditional phytosanitary controls, can have serious effects on ecosystems and biodiversity conservation.

In addition to pathogens, invasive microbial species and strains may also be introduced. These may predate or replace existing species, possibly triggering a cascade effect. Because of the possibility of using synthetic biology to incorporate novel nucleic acids into pathogens and other organisms, such potentially harmful and invasive species are at least equally, and may be even less predictable, than LMOs transformed with better-characterized transgenes.

It is reasonably expected that the time necessary to synthesize organisms from sequence data will continue to shorten, and that the lengths of functional genomes that may be practically synthesized and cultured will continue to grow. It is also reasonably expected that the facilities with the resources and capability to create such synthetic organisms will continue to grow in number and geographic extension.

6. Best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments, including transboundary movement, to inform those who do not have national risk assessment or monitoring regimes, or are in the process of reviewing their current risk assessment or monitoring regimes

The "Guidance on Risk Assessment of Living Modified Organisms", developed, updated, improved and tested by two iterations of the Ad Hoc Technical Expert Group on Risk Assessment under the Cartagena Protocol on Biosafety over the past six years (2008-2014) provides best practice guidance on risk assessment and monitoring, in relation to LMOs. The Guidance comprises a "Roadmap for Risk Assessment of Living Modified Organisms", four guidance documents on specific types of LMOs and traits and guidance on monitoring of LMOs released into the environment. Discussions are currently ongoing as to whether to provide further guidance on specific techniques or modification process, including for risk assessment of LMOs produced through synthetic biology.

It should be noted however, that the Guidance is limited to LMOs, and does not fully address the risks of organisms, products and components arising from synthetic biology. This points to a gap in risk assessment and monitoring regimes for synthetic biology.

7. The degree to which the existing arrangements constitute a comprehensive framework in order to address impacts of organisms, components and products resulting from synthetic biology relevant to the objectives of the Convention on Biological Diversity and its Protocols, in particular threats of significant reduction or loss of biological diversity

A detailed overview of existing arrangements is needed.

In the United States, which is not a CBD Party but is a key county for synthetic biology research, laboratory safety arrangements for synthetic biology lack the force

of law. Recommendations for synthetic biology laboratory safety have been incorporated into national government guidance (the National Institutes of Health Guidelines), however, many facilities – including almost all of the private sector – are under no obligation to follow this safety guidance.

Moreover, of the subset of facilities that are under an obligation to follow the federal guidance for synthetic biology research safety (generally implemented through stipulations in research funding contracts), peer reviewed research has shown that noncompliance is a serious problem (see: Biosecur Bioterror. 2008 Mar; 6(1):19-35).

This indicates two serious, and related, problems. First, there is insufficient oversight of individual scientists, particularly with respect to the projects that they choose to perform, leading to a situation where individual researchers inappropriately judge the safety of their own studies. Synthetic biologists may lack the knowledge and inclination to properly assess the potential impact of their research, including the impact of both intended results and incidental ones and accidents, on biodiversity and human health.

Secondly, facilities conducting synthetic biology research are, in general, not legally overseen per se, and are not, for example, required to obtain a license in order to perform synthetic biology activities. This may lead to inadequate and variable safety conditions.

Possession of a very small number of particularly dangerous organisms, including a number of microoganisms that may be generated by synthetic biology techniques, is covered is the United States by a binding licensing regime (a "select agent permit"), however, the US methodology of maintaining a list a specific pathogens possession of which triggers the rule, is poorly adapted to and cannot be effective applied to synthetic biology. This is because creation and possession of synthetic organisms incorporating even quite small nucleic acid changes that may be introduced by synthetic techniques fall outside the scope of activities covered by the licensing regime, even if the synthetic pathogens maintain (or even worsen) the potential effects on biodiversity and human health of their unmodified analogs.

8. Information on measures undertaken in accordance with paragraph 3 of the decision, including the identification of needs for guidance

Parties to the Cartagena Protocol on Biosafety have taken the necessary and appropriate legal, administrative and other measures to implement their obligations under the Protocol. However, as pointed out earlier, gaps still remain in terms of the adequacy of existing national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques; risk assessment and monitoring regimes for synthetic biology; and existing arrangements to address impacts of organisms, components and products resulting from synthetic biology. Therefore, there remains a need for further guidance in relation to organisms, components and products resulting from synthetic biology, particularly as these make up a broader category than LMOs.