Submission of Information on Synthetic Biology

in response to CBD Notification 2015-013

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a) Information that is relevant to the work of the AHTEG, including views on:

(i) How to address the relationship between synthetic biology and biological diversity;

The relationship between Synthetic Biology and Biological Diversity is multi-faceted, including the fact that SB is based on and derived from biological systems, utilises biological (including genetic) resources and functions (largely) within biological systems, parameters and constraints.

> However, underpinning synthetic biology is a comparatively new assumption: that living organisms can be assembled from parts and that parts can also be removed from organisms, or adjusted, and leave the organism still able to function and it or its interactions with the environment not affected in unpredictable ways. Claims include that such modifications can 'improve' the 'functions' of the organism. Organisms are being referred to as machines in which to install genetic circuits. This means that synthetic biology is increasingly based on the metaphor of engineering. This is fundamentally different from biology, in which the parts of an organism, the organism and the ecosystem are interdependent and affect each other in ways that we only partly understand. Furthermore, organisms replicate, adapt, evolve and are subject to mutations, which sets them apart from engineered entities. These mutations may or may not be helpful to the organism in the context in which it lives and evolves We also know that the process of genetic engineering, with which synthetic biology considerably overlaps, itself generates unpredictable off-site mutations.
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> Another metaphor which is rapidly altering our perceptions and relationships with living organisms is that of computing. Computers can be used to generate gene sequences, but the terminology of computing is being extended to organisms, while organisms and their parts are also being recruited for developing new generations of computing. This cross-over is fascinating but brings its own perils in the form of changed attitudes towards organisms, ecosystems and biological processes. There is a serious risk that they will increasingly be seen as mechanical, linear processes to be mined for information, so neglecting multifunctionality and the interrelationships between the 'parts'.

It would be beyond the scope and capacity of an AHTEG to fully address all aspects and facets of the relationship between Synthetic Biology & Biological Diversity. Instead, focus should be given to those areas that are of concern – within the context of the CBD - and that can negatively impact biological diversity, human health, small scale farming systems and their contribution to biological diversity and ecosystem function, food security, livelihoods and related socioeconomic considerations, indigenous peoples and local communities, including cultural aspects.

(I) A systematic, multilayered and interrelated approach to this would be helpful and relationships of concern addressed should include:

(1) Direct contact through intentional or unintentional release into the environment (water, land, air):

- organisms resulting from synthetic biology
- compounds resulting from synthetic biology and
- products resulting from synthetic biology

Some of these may be new compounds and products not previously present in or released into the environment or not in this quantity, purity or combination. The problems arising from mass production and mass release is part of this concern (we recall for example the unforeseen and increasing burden and negative impact of plastic, particularly when it breaks down into very small particles, but also bags and bottles etc on aquatic life):

a) in their intended and well characterised manifestation/form
b) in unintended / unexpected form (including precursors)
c) in altered form: eg breakdown products (in numerous cases breakdown products are more harmful than the original compound/substrate, eg some fire-retardants); shortened or unexpected dsRNAs; genetic or synbio elements and compounds integrated by other organisms; alterations occurring through interaction with organisms, compounds and conditions present in the environment.

<u>Invasive Alien Species:</u> Invasive alien species are already of serious concern to the CBD for their impacts on biodiversity in many parts of the world. There is a very real risk that organisms produced through the use of synthetic biology techniques could become invasive alien species, posing a completely new level of risk to biodiversity, especially if there are no comparators to use to assess their impacts (see re comparators below). Alien Invasive Species in this context refers to any organisms, plant, animal, fungus or microorganism.

(2) Direct contact (either intended or unintended) by/between humans and organisms, compounds and products resulting from synthetic biology, either in the open environment or at the workplace, with any of the permutations detailed above under (1).

(3) Indirect impact: Feedstock requirements

Here we are looking at requirements for large scale production systems with contained use applications of SB microorganisms, including algae, or SB processing aids. Feedstocks are thought likely to be largely made up of carbohydrates (eg sugars/starch/cellulose) which may be sourced eg from sugar cane, sugar beet, corn, tree plantations, etc., which may be LMOs or not. Their large scale production has been and/or may be linked to:

a) land issues: land rights and land use change
b) water issues
c) problematic use of chemicals (eg pesticides) and chemical pollution, detrimental to biological diversity, ecosystem function and human health
d) working conditions issues

e) food security/sovereignty (where people are surrounded by sugarcane plantations their access to food and land for food may well be diminished)

(4) Genetic resources:

Where a technology requires the production of feedstocks, there are implications for biological diversity, but also for agricultural biodiversity and local food security, since where people are driven off the land, their local crops and knowledge are also displaced and often lost.

Another aspect of genetic resources in the context of synthetic biology is access and benefit sharing (addressed through the Nagoya Protocol), which is not only about the sourcing of the genetic material in situ, but also about digital sourcing or the combination of known sequences through computing, yet producing a substance that may replace natural products produced by and representing livelihoods to indigenous peoples, local communities and small scale farmers.

(5) Replacement of products and

a) impact on livelihoods
b) impact on small farming systems (see point 6).

(6) Impacts on small farming systems and their contribution to biological biodiversity, maintenance of ecosystems, micro-climate and water capture.

Smallscale agriculture still feeds the majority of the human population. In addition to this, it is also clear that successful smallscale farming systems that do not or cannot rely on the use of chemicals, whether fertilisers or pesticides, are vital for maintaining biodiversity and agricultural biodiversity in situ. Increasingly, agroecological practices which can include smallscale organic, permaculture and biodynamic systems are recognised as the most successful ways to maintain soils, their quality and health, to prevent soil degradation and soil erosion and also to protect and regenerate water resources. They are also important to maintaining and improving beneficial local micro-climates.

(7) Impacts on indigenous peoples and local communities, including also cultural aspects.

It is clear that synthetic biology could have a major effect on indigenous people and cultural and spiritual aspects through: contamination of biodiversity; loss of land to eg: sugar production as feedstock for synthetic organisms; and the changing relationship between human beings and the biosphere exemplified by the application of the engineering metaphor to life, which implies that human beings have both the capacity and the right to engineer living organisms for human purposes.

This is a crucial aspect and one which requires the full participation of indigenous peoples and local communities. Thus it cannot be a matter that is rushed but one where time is given.

(8) Synergistic, cumulative and combinatorial effects

Quite apart from the potential impacts of particular aspects of synthetic biology, we have the unknown and often impossible to predict impacts of interactions between different aspects/elements involved. Synergistic, cumulative and combinatorial effects have been discussed in the context of environmental release of LMOs as well

as stacked gene events, but also in the context of pharmaceutical compounds and manmade chemicals present in the food chain. Now it is a known fact that if a substance A is safe to consume (or to apply) at a certain level, and so is a substance B, this does not mean that A and B in combination would be safe. Indeed, on occasions, such combinations have been shown to be toxic.

(II) Liability and Redress

It should be assured that damage arising from organisms, components and products resulting from synthetic biology techniques is addressed through a liability and redress regime.

(III) Another area of concern is that of **"contained use"**, the concept of functional separation of organisms from the environment. This has proven to be a flawed concept. Experience shows that so-called contained use systems and facilities are mostly leaky systems. This applies both to physical installations of industrial facilities and to genetically engineered 'contained use' concepts such as Terminator-type technologies (V-GURTs) and engineered 'unfitness' to fail to survive outside conditions. Organisms, have a tendency to adapt and evolve in order to survive and reproduce, especially micro-organisms, which often exchange information through horizontal gene transfer. And industrial facilities are not proof against human error, system failures, material breakage and extreme environmental conditions and events. Given the quantity and often new qualities and makeup of organisms, compounds and products resulting from synthetic biology, rigorous risk assessment encompassing all aspects (see section I above) should be performed for all applications, irrespective of whether intended for contained use or not. It should always be recalled that one escape could potentially be catastrophic and irreversible, even if the likelihood of it occurring is extremely low.

(IV) In this context we would like to draw attention to the need of strict application of the **precautionary principle**, as recently discussed in Taleb et al. (2014), who for example state:

"The precautionary principle (PP) states that if an action or policy has a suspected risk of causing severe harm to the public domain (affecting general health or the environment globally), the action should not be taken in the absence of scientific near-certainty about its safety. **Under these conditions, the burden of proof about absence of harm falls on those proposing an action, not those opposing it."**

(V) In view of the assertions that genetic engineering and synthetic biology are becoming ever more precise, and the assumption derived from that is that the results will therefore be more predictable/stable/safe, it would also be of importance to address this concept of **"precision".** In particular we need to examine to which extent this "precision" can reliably be extrapolated from the minute molecular level, such as a specific genetic sequence alteration, to the cellular and organism level and from thence to the macro level of ecosystems. We would suggest that such an extrapolation is false and holds danger. This assumption of precision and hence of predictability constitutes a false perception of the relationship between synthetic biology and biological diversity and ecosystems.

Knowledge & precision at the level of nucleotides is only the bottom layer.
What is missing is any contextualisation into:

- the genome

- the epigenetic landscape
- the organism
- the ecosystems
- the socio-economic conditions that differ around the world

This urgently needs addressing.

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

Organisms, components and products of synthetic biology techniques cover a much wider range than LMOs, as LMOs clearly only refer to Living Organisms, not to components or products.

For example, synthetic biology also utilises cell free systems containing genetic information/sequences, which thus do not fall under the definition of an LMO. However, DNA or RNA would still be readily available for appropriation by other organisms from such cell free systems which would very likely not be regarded as 'biological entities' (see use of terms for 'living organism, Cartagena Protocol on Biosafety).

Article 3 (Use of Terms) of the Cartagena Protocol states:

g) "*Living modified organism*" means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology;

(h) "*Living organism*" means any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids;

(i) "*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;

Given the current availability and utilisation of techniques of **"modern biology",** the majority of organisms resulting from synthetic biology would at present be covered by the definition of an LMO, but this is not true of all. The definitions under article 3 (see above, especially underlined sections) limit the extent to which a modified organism may be called an LMO. The definition of "modern biotechnology" with the proviso of "that overcome natural physiological reproductive or recombination barriers" creates a substantial grey zone with much room for interpretation, with some organisms resulting from synthetic biology clearly not being covered – and thus not being eligible as an LMO.

Epigenetic changes are excluded from cover

For example, organisms with epigenetic changes introduced through transient delivery of dsRNA resulting in gene silencing over at least a number of generations (RNA-dependent DNA methylation (RdDM)), do not fall under the definition of LMOs (as defined in the Cartagena Protocol), as there is, for example, no "novel combination" of genetic material. The methylation of the Cytosine nucleotide for example does not change the DNA sequence

but rather prevents the gene from being activated and transcribed. Thus no AIA and no risk assessment would be required – irrespective of risks and potential negative impacts.

Playing with definitions to avoid 'the burden of' regulation
Furthermore, moves are now afoot to have GMOs resulting from certain in vitro nucleic acid techniques and applications excluded from the European GMO regulations based on legalistic arguments that they do not meet the definitions of a GMO (eg NBT Platform, April 2014).[1] This is also where it is clearly very important to ensure that the **process** of engineering a GMO is considered in any assessment. To consider only the **product** and not the **process** involved, as is preferred by some, is failing to recognise that the process itself does lead to quantitative and qualitative changes, other than just the "addition" of the intended trait. Non-target effects as well as transformation induced mutations, but also pleiotropic effects of an introduced gene or regulatory interference are sufficient reasons for all genetically engineered organisms –irrespective of definitions- to undergo a full risk assessment and require an AIA. In this, the technology has to remain as the trigger for risk assessment, and irrespective of similarities or differences between LMOs and "organisms, components and products of synthetic biology techniques", the task and obligation is to ensure that non slips through the net of risk assessment and AIA requirement either due to insufficient definitions or misconceptions of risk.

Similarities between LMOs and organisms resulting from synthetic biology lie largely in the use of the same or similar techniques of in vitro nucleic acid techniques resulting in the modification of the genetic material of an organism. However, the vocabulary and concepts used are at times quite distinct and indicate a very different mindset and approach to organisms, living systems, their integrity and their place within biodiversity, eg by referring to organisms as machines, with all the assumptions about human control and instrumentality inherent in this metaphor.

(iii) Adequacy of existing national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques;

To assess the adequacy of existing instruments to regulate the organisms, components or products derived from synthetic biology techniques, two conditions need to be met:

a) an overview of all the instruments that cover or could cover the various aspects necessary to regulate organisms, components or products derived from synthetic biology techniques in line with the CBD decisions
b) to have in place the criteria to assess adequacy for all the protection goals and aspects specified in the CBD decision and CBD obligations, including socio-economic aspects, impacts on livelihoods, indigenous peoples and local communities, food security, small scale farming and its contribution to feeding populations and maintaining biodiversity, amongst others (see also comments to point i)

Adequacy would also require the integration of or communication between national, regional and international instruments to ensure that synthetic biology related activities in

[1] [www.infogm.org/IMG/pdf/nbt-plateform_statut-ogm_avril2014.pdf]

one location or party do not negatively impact biodiversity, livelihoods, socio economics, food security, indigenous peoples and local communities etc elsewhere.

(iv) An operational definition of synthetic biology, comprising inclusion and exclusion criteria;

There have been many attempts to define Synthetic Biology. It is clearly possible to regulate an issue that does not have a conclusive definition. Such regulation is actually normal because there is no conclusive definition of a gene, a forest, or even biodiversity. It is possible to fight biodiversity loss before the last taxon or species has been defined.

It is thus important to not get caught up in attempting "the perfect" definition.

We thus fully support the idea of an operational and "evolving" definition where the whole focus is on defining Synthetic Biology in itself, but one that will ensure that all technologies currently used or to be developed in the future, related to synthetic biology, are included in principle, and that such technologies and techniques are linked to the definition through an continuously updated list or appendix.

We see the purpose of such an operational definition to be to ensure that none of the technologies and applications (and the resulting organisms, components and products) accidentally escape an assessment just because the definition is too narrow or too quickly outdated.

Our understanding, our technologies and our ability to modify living systems, nucleic acid sequences and composition (incl. the utilisation of novel nucleotides), organisms, biological processes and their constituents (such as proteins and membranes, including the creation of novel amino acids) according to design have changed and grown since the use of terms were debated and agreed for the Cartagena Protocol in the late 1990s. We are currently living in a time where developments in technology are constantly moving ahead of our capacity to understand the implications of any one development, and especially of the interactions between different developments and in turn, their interactions with living systems.

(v) 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;

For us there are many aspects to this topic, that all require addressing, often in a multi-layered manner, in order to fulfil parties' obligations under the convention and to fulfill the mandate of the last and previous COP decisions.

In the following we will focus on the question/topic of potential harm and risks arising from the development, use and production of organisms, components and products arising from synthetic biology techniques. Whilst we recognise that there is a need for a thorough assessment of claimed or potential benefits if one wants to see or ensure that these benefits indeed arise, and if so for how long and to whom, it is not our field of expertise. We do not feel able to comment on potential benefits while there are so many risks and above all, so

many unknowns, in connection with synthetic biology. Furthermore the notion of the need for synthetic biology involves predictions in which there are also too many unknown factors for it to be possible to speak meaningfully.

Furthermore, we regard it as a primary obligation and task to address potential harm and negative impacts, as those pose a threat 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;

In overview:

1) Identification of potential harm and risk

a) This must be done separately and in combination for all three categories: ie. (i) organisms, (ii) components and (iii) products arising from synthetic biology techniques. Potential harm, risks and risk questions may change depending on whether it is an organism, compound or product.

b) It must be done separately for all the different aspects as outlined under submission question (i) our point (I), which includes the conservation and sustainable use of biodiversity, and negative impacts on human health, food security, small scale farming systems (and their contribution to biological diversity and ecosystem function), livelihoods and related socioeconomic considerations, indigenous peoples and local communities, including cultural aspects. Related to this are issues of water, land rights, land use change, micro-climate, genetic resources and intellectual property.

c) **Identification of location /place/community** of potential harm, as it might be outside the national boundaries of the party/non-party of production or the party/non-party of use. This would for example be the case where products of synthetic biology would be replacing on the national or international market the (natural) products of small farming systems elsewhere and/or negatively impact livelihoods, farming systems, food security etc. and related biodiversity and ecosystems. These could be oils, fragrances and flavours, medicinal substances etc.

d) **Whole life cycle analysis:** It is difficult to encompass the whole breadth of potential harm that can arise from the development, use or production of organisms, components and products arising from synthetic biology techniques. It would thus be helpful to produce frequent full life cycle analyses to provide the data and insight where harm arises. For example the issue of feedstocks. Where the production of oils through micro-organisms, here algae, requires the constant input of sugars – these sugars need to come from somewhere. Whether corn syrup or cane sugar, it will require land and inputs to produce them, which in turn may be linked to issues of water, soil, land rights, land use change, chemical applications – which in turn have the potential to negatively impact the conservation and sustainable use of biodiversity and related human health and socioeconomic impacts relevant to the mandate of the Convention and its Protocols.

2) Assessment of risk.

The overall risk assessment would be for all the potential harms identified above combined. It would however be made up of numerous specific risk assessments, such as under (a) above for (i) organisms, (ii) components and (iii) products arising from synthetic biology techniques done separately for all the different scenarios identified.

In cases where an organism arising from synthetic biology falls under the definition of an LMO as defined by the Cartagena Protocol, the Articles, Annexes and provisions of the protocol should apply, as well as those of its Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress. The Cartagena Protocol though only covers transboundary movement, primarily intentional transboundary movement. It has reduced requirements (ie no AIA) for LMOs in transit or destined for contained use.

The Cartagena Protocol risk assessment however cannot suffice as the only risk assessment for LMOs arising from synthetic biology techniques, as a) it does not cover domestic use or production nor b) does it cover the same breadth of impacts as mandated by the COP decision(s).

The Cartagena Protocol also does not cover components and products arising from synthetic biology techniques (unless they should fall under the definition of LMOs).

Furthermore, as identified by parties to the Protocol, there is a need for further guidance for risk assessment and risk management of LMOs that are micro-organisms, including algae, and for LMOs that are produced through synthetic biology techniques. When performing a comparative risk assessment, there is a need for a 'comparator', which may not readily be available for organisms derived through synthetic biology.

We find that at present there is insufficient risk assessment and risk management capability/capacity for organisms, components and products arising from synthetic biology techniques, regarding their impact on the conservation and sustainable use of biodiversity and related human health, socioeconomic and cultural impacts relevant to the mandate of the Convention and its Protocols;

We would like to underline that synthetic biology techniques, such as genome editing, epigenetic alterations (including external application of dsRNA), gene drive systems, metabolic pathway engineering – including photosynthesis engineering, cell free system applications, ribosome engineering, cell-membrane engineering, production of newly designed nucleotides (xeno-nucleotides) and amino acids, are qualitatively very different and a noticeable step change from previous methods and applications of genetic engineering. This is particularly the case when overlaid with the notion of synthetic biology as a pure and rational engineering approach, that will make living systems controllable and predictable. There is a serious knowledge gap that needs to be closed for reliable risk assessments, including assessing the assumptions of precision and predictability in living systems.

3) Collaboration across borders, disciplines and jurisdictions

Collaborations (across eg: borders, topics and disciplines) are essential to identify and understand the nature and place of potential harm and to assess risks over time and across borders, also to produce full life cycle analyses over time and across borders, to know which questions to ask and which indicator to use.

(vi) 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;

Under the Cartagena Protocol on Biosafety a best practice guidance for risk assessment and risk management of LMOs was developed by the AHTEG on Risk Assessment and Risk Management of LMOs during 2008 – 2014. Entitled "Guidance on Risk Assessment of Living Modified Organisms" (https://bch.cbd.int/protocol/guidance_risk_assessment), the guidance is made up of Section I: "Roadmap for Risk Assessment of Living Modified Organisms", Section II: "Types of LMOs and Traits" (with four detailed documents) and Section III: "Monitoring of Living Modified Organisms Released into the Environment". This guidance has been tested, revised and improved over the years, and is considered to be a living document, with further guidance still to be developed on specific LMOs, most urgently for LMOs introduced in centres of origin and genetic diversity, LM microorganisms and viruses and LM fish.

Whilst "Risk assessment of living modified organisms produced through synthetic biology" is also listed as a topic that requires further guidance, it only refers to "LMOs" as defined under the protocol. Importantly, the Cartagena Protocol does not cover compounds and products, nor does it cover organisms arising from synthetic biology techniques that fall outside its definition.

(vii) 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;

To the best of our knowledge, existing arrangements do not constitute a comprehensive framework to address impacts of organisms, components and products resulting from synthetic biology in line with the obligations under the Convention and its protocols.

On the contrary, there are attempts to sidestep or evade current GMO regulations either by seeking exemptions (eg genome editing) or by declaring that practices and applications fall outside current definitions of LMOs or GMOs (eg RNA dependent DNA methylation). Both these examples are techniques of synthetic biology.

(b) Information on measures undertaken in accordance with paragraph 3 of the decision, including the identification of needs for guidance;

Multilayered, interdisciplinary and cross-boundary risk assessments are required for avoiding significant negative impacts from the development, production and use of (i) organisms, (ii) components and (iii) products arising from synthetic biology techniques.

Given that synthetic biology is a new field whose technologies are being rapidly developed and applied, and given that synthetic biology takes a very different approach to organisms and living systems as compared to biology and ecology, and given also the significant spectrum of knowledge and understanding required to identify potential harm as well as to assess the actual risks, it will not be easy to develop and/or carry out risk assessments that can fulfil the requirements stated in the COP mandate and also entailed by the obligations under the Convention.

We hence see that there is a lack of guidance materials for both an overall risk assessment and also for the individual categories and layers previously detailed and this gap needs to be filled before any proper risk assessment of synthetic organisms can be carried out.