CropLife International comments on CBD peer-review of synthetic biology outcomes

Documents:

- UNEP/CBD/SYNBIO/AHTEG/2015/1/2 – Updated Report and Synthesis of Views in Response to Paragraph 7(b) of Decision XII/24 on New and Emerging Issues: Synthetic Biology
- UNEP/CBD/SYNBIO/AHTEG/2015/1/3 – Report of the Ad Hoc Technical Expert Group on Synthetic Biology

UNEP/CBD/SYNBIO/AHTEG/2015/1/3

Para 20 (and para 24)

We agree with the essence of this paragraph that synthetic biology encompasses multiple disciplines from which tools and techniques may be applied for various purposes and end products. However, we believe it is more appropriate to describe synthetic biology as a continuum of modern biotechnology, rather having "a degree of overlap" with it. We therefore generally agree with the views in paragraph 25 of UNEP/CBD/SYNBIO/AHTEG/2015/1/2, and disagree with the views in paragraph 26 that synthetic biology is quantitatively different to modern biotechnology.

Para 21

We agree that the "operational definition" should be understood in the context of the CBD objectives and recommend that this should be the scope of deliberations on all of the synthetic biology topics addressed in this forum.

Para 22 (and para 24)

The synthesis provided in UNEP/CBD/SYNBIO/AHTEG/2015/1/2 indicates support for the synthetic biology definition published by the three scientific committees of the European Commission in the AHTEG (UNEP/CBD/SYNBIO/AHTEG/2015/1/2, paragraph 32), which was also supported by some members of the AHTEG (paragraph 22). The definition ultimately produced is largely the same apart from several additions made by the AHTEG that we question in regard to necessity and/or appropriateness.

For comparison, the definition of the three scientific committees concisely states the following: "SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms."

The operational definition of the AHTEG adds the statement that synthetic biology is "a further development and new dimension of modern biotechnology". We do not agree with this phrase as it incorrectly infers that synthetic biology is something completely novel; rather than the definition expressing "the notion of continuity and novelty" as referred to in paragraph 22, it is emphasising and overstating the "novelty" aspect. This is also inconsistent with many views expressed in the online discussions (e.g. paragraph 25, UNEP/CBD/SYNBIO/AHTEG/2015/1/2). We agree that synthetic biology is a "further development", but in the sense that it is part of a continuum of advancement in modern biotechnology, and this phrase does not capture this "continuity" aspect. Additionally, this definition will not remain relevant longer-term due to this phrase reflecting the views of some at this current point in time.

We agree with the addition of the word "understanding" to the definition, as an important application of synthetic biology approaches today is the understanding of living systems. We do not agree that the word "redesign" is necessary, as both "design" and "modification" capture this.

If there is agreement that synthetic biology is an application of modern biotechnology that combines science, technology and engineering to facilitate the understanding, design, manufacture and/or modification of genetic materials in living organisms, and as such is encompassed in the definition of modern biotechnology, then one might ask whether there is a need to define synthetic biology. It could be simply acknowledged that products from synthetic biology approaches belong to the category of "products of modern technology".

Para 27

We agree that considerations of the impacts of synthetic biology applications, in the context of the CBD's objectives, need to be evidence-based. We also support the need for evidence of a certain scientific standard like peer-review in reputable scientific journals. We agree that different types and sources of information may be relevant to these considerations, however synthetic biology is inherently highly technical and insufficient weight has been given to scientific knowledge, data and experience in this paragraph. As stated above, synthetic biology is a part of a continuum of technological advancement in modern biotechnology and it is not completely new, and consequently there is a wealth of highly relevant and published scientific evidence, and any consideration should include a comprehensive review of the relevant scientific literature.

Para 28 (and para 27)

We question the approach taken in this forum to separate the living organisms created by synthetic biology and the non-living components and products of synthetic biology for consideration. We do not agree that the living organisms and non-living components and products can impact on all three CBD objectives; for example, how does a component used in a synthetic biology application impact on *any* of the three objectives – arguably only tenuous connections can be made. This emphasises our point in relation to paragraph 27 that there needs to be rational, evidence-based consideration of potential impacts, rather than speculation.

Para 29 (and para 27-28)

We do not agree that a higher level of uncertainty is the inevitable consequence of an "increased depth of intervention" (also referred to in paragraph 44). It is not clear what exactly this statement is referring to, i.e. "increased" compared to what baseline, what "depth of intervention" means, and why there should be a connection between these and adverse impacts on biological diversity. This again highlights the importance of our point in relation to paragraphs 27 and 28 that any consideration of potential impacts needs to be realistic, and based on relevant evidence and not speculation.

Uncertainty is inherent in science and should not be managed with disproportionate measures that hinder innovation. We agree with the statement in this paragraph that existing risk assessment frameworks already assess uncertainty. Ideally this is managed by undertaking further research and/or through the implementation of proportionate risk management strategies, such as containment and monitoring, that evolve (i.e. reduced containment) with improved understanding of the potential impacts of the technology on biological diversity. We also agree with the statements that the risk assessment of living organisms created by synthetic biology approaches will be assisted by the wealth of existing experience with modern biotechnology and that greater predictability of outcomes may be possible with synthetic biology. These are advantages that will contribute to the assessment and mitigation of uncertainty.

Para 30 (and para 27-29)

We find the assumption that synthetic biology applications are evolving at a rate that will overwhelm regulators and decision-makers such that they will not be able to fully address the potential impacts a completely subjective proposition . Apart from this being speculative and

reaching beyond the scope of deliberations (i.e. the three CBD objectives), for such statements to be considered, they should be supported by evidence.

Furthermore, the difference between the speed of technological development and the need for risk assessment should be recognised. The paragraph implies that the rate of technological development is equal to the potential for biological diversity to be exposed to living organisms created by synthetic biology approaches and the components and products of synthetic biology. This is inconsistent with the reality that most foreseeable synthetic biology applications are intended for contained use.

This paragraph also refers to "indirect effects" of the living organisms and non-living components and products of synthetic biology. As stated above for paragraphs 27-29, we emphasise that any consideration should be evidence-based and not driven by speculation, and the reason that this is raised should be explained.

Para 31 (and paras 39, 52)

This paragraph (and others) refers to the use of digital information (e.g. DNA sequence) and the potential for its "inequitable use". It is evident in paragraph 52 ["potential adverse effects" objective 3, paragraph (l) and (m)] that there are members of the AHTEG promoting the referred to "shift in the understanding of what constitutes a genetic resource" in order for the use of DNA sequence information to constitute "misappropriation" or "inappropriate access without benefit sharing".

It is noted in paragraph 39 that there is a lack of clarity in how the access and benefit sharing provisions of the CBD and Nagoya Protocol may apply to synthetic biology. The CBD provides definitions of "genetic resources", "genetic material", "biological resources", and "biotechnology", and the Nagoya Protocol defines "utilisation of genetic resources". None of these definitions are exhaustive lists and all are open to interpretation. The use of DNA sequence data is not new to synthetic biology; it has long been used and exchanged within the modern biotechnology scientific community. Attempts to expand the interpretation of definitions in CBD/Nagoya framework to include DNA sequence data is fraught with problems: it expands the obligations of Parties to the Nagoya Protocol beyond that which they agreed to, but have the discretion to impose at the national level, as well as the discretion to impose in individual agreements; it will stifle innovation and product development by restricting access to the necessary information and creating legal uncertainty around its use; and it would be impossible, and simply unrealistic, to attempt to track every use of every part of a DNA sequence, for example, many parts of DNA sequences from many different species could be used in one synthetic biology application, and the sequences used may be

shared by many different species. It is also questionable if the Parties to the Nagoya Protocol intended for such a restrictive application of its obligations, and for access and benefit sharing obligations to apply indefinitely.

Para 34

We support the conclusion of the AHTEG that living organisms created by synthetic biology approaches are similar to LMOs as defined by the Cartagena Protocol, however we believe that these organisms *are* LMOs rather than "similar to". This is also stated in paragraph 66(b) (conclusions). Such organisms are LMOs by virtue of their creation using "modern biotechnology" as defined by the Cartagena Protocol. We therefore agree with the views in UNEP/CBD/SYNBIO/AHTEG/2015/1/2 that the LMO definition in the Cartagena Protocol is readily applicable and sufficiently broad to include living organisms created by synthetic biology (paragraphs 31 and 46).

Para 38

The paragraph refers to "many" non-living components and products being within the scope of the CBD but not the Protocols (Cartagena Protocol and Nagoya-Kuala Lumpur Supplementary Protocol) and possibly not national biosafety frameworks. The scope of international and national frameworks that are applicable to the non-living components and products of synthetic biology have not been comprehensively examined in the online discussions, information submissions or the deliberations of the AHTEG. Therefore, conclusions cannot be drawn by the AHTEG beyond the fact that the Protocols referred to are only applicable to the living organisms created by synthetic biology, and that relevant sectoral frameworks for the various types of expected products of synthetic biology (e.g. chemicals, pharmaceuticals, veterinary products) exist, as noted in paragraph 40 (also paragraph 49 of UNEP/CBD/SYNBIO/AHTEG/2015/1/2). There appears to be greater consideration of the applicable existing frameworks in the online discussions (e.g. paragraphs 49-50 and 57(j), UNEP/CBD/SYNBIO/AHTEG/2015/1/2) than by the AHTEG. It should also be noted that such frameworks are supplemented by the obligations of the CBD for Parties to, for example: "[d]evelop national strategies, plans or programmes for the conservation and sustainable use of biological diversity" (art 6(a)), to "[i]ntegrate as far as possible and as appropriate, the conservation and sustainable use of biological diversity into relevant sectoral or cross-sectoral plans, programmes and policies" (art 6(b)), and to implement various measures aimed at biological diversity conservation (art 8) and sustainable use (art 10).

Para 40 and 41 (and para 38)

It should be remembered that any consideration of "needs" in relation to an international regime should be consistent with the scope of the three CBD objectives. In regard to non-living products and components, as stated above for paragraph 38, there has been no comprehensive examination of the scope of international and national frameworks applicable to the non-living components and products of synthetic biology by this forum, therefore no conclusions can be drawn on whether or not these include socio-economic considerations, or whether these are even relevant or appropriate in the context. For this reason, we do not agree with the assertion that this is a "need" and with the assertion in paragraph 61 that existing frameworks do not adequately deal with such considerations.

We also disagree with the assertion that there is a need for international regimes for trans boundary movements of living organisms created by synthetic biology, since these are LMOs and already within the scope of the Cartagena Protocol and the Nagoya-Kuala Lumpur Supplementary Protocol which specifically cover trans boundary movements, and benefit sharing in relation to the use of genetic resources which is the subject of the Nagoya Protocol. Such regimes would be duplicative of these existing Protocols, and would simply be attempts to coerce Parties to agree to expanded obligations which they already have the discretion at the national level to implement. For example, in regard to "traceability", the Nagoya Protocol provides: "[e]ach Party shall take legislative, administrative or policy measures, as appropriate" (art 5), with the aim of ensuring that benefits arising from the utilization of genetic resources are shared. This gives Parties the discretion to implement requirements at the national level that are applicable to their circumstances.

Para 42 (and para 60)

As stated above, there has been no comprehensive examination in the online discussions, information submissions or the deliberations of the AHTEG, regarding the application of international or national frameworks to the non-living components of synthetic biology. We also question whether such regulation is "adequate or even needed" as stated in paragraph 60. As stated above, synthetic biology utilises the tools, including components, of modern biotechnology. It was not considered necessary to separately consider and regulate these tools under the Cartagena Protocol. Further, biosafety regulation is not limited to the Cartagena Protocol, with the trans boundary movement of such (non-living) biological materials or chemicals subject to other international and national frameworks. At the international level these include, for example, the UN Model Regulations for the transport of dangerous goods that cover the transportation of

chemicals and other materials that are deemed hazardous, and these are intended to be integrated into all modal and national regulations for an internationally harmonised approach.

Para 45 (and paras 44, 20, 24, 29, 59)

We do not agree with the statement that a "distinctive quality" of synthetic biology is the "rate and depth of intervention" compared to "classical genetic engineering". This appears to expand the definition provided in paragraph 24, and is an assumption that needs to be qualified. As stated in paragraph 20, synthetic biology is a broad term, and it encompasses a range of applications, which cannot be clearly distinguished from applications of modern biotechnology.

This paragraph also speculatively links increased genetic modification with increased uncertainty in risk assessment. As stated above for paragraph 29, existing risk assessment frameworks already deal with uncertainty on a case-by-case basis, and assessment of living organisms created by synthetic biology approaches will be assisted by the wealth of existing experience with modern biotechnology and greater predictability of outcomes possible with synthetic biology (also consistent with the views in UNEP/CBD/SYNBIO/AHTEG/2015/1/2, paragraph 40). The risk assessment framework of the Cartagena Protocol already advocates a case-by-case approach which includes the identification of suitable comparators, which may include more than one comparator and other modified organisms where appropriate. Further, the risk assessment framework of the Cartagena Protocol does not prescribe that only a comparator-based approach should be used, therefore alternative approaches may be considered or required depending on the LMO. We therefore disagree with the assertion that "challenges in establishing meaningful comparators" presents a "gap" in existing risk assessment methodologies in paragraph 59, and agree with the statements in paragraphs 46 and 48 that assessment should be on a case-by-case basis taking into account the particular circumstances of the synthetic biology application.

Para 49

The report indicates on one hand '*the potential* 'to engineer more complex organisms (Para 4) and on the other hand 'due to its higher level of complexity'. The use of 'can be' versus 'must be' is inconsistent here. In case of 'must be' there should also be argumentation as to why synthetic biology is more complex.

Para 50

We agree with the essence of this paragraph that appropriate science-based methods should be used where socio-economic considerations are to be taken into account in the assessment of the potential impacts of synthetic biology. However, we emphasise that any consideration of socio-economic considerations should be at the discretion of the Party and not prescribed by an international framework. Socio-economic considerations *may* be taken into account in regard to decision-making concerning the living organisms created by synthetic biology (LMOs) under the Cartagena Protocol (art 26). As stated above for paragraphs 40 and 41, there has been no comprehensive examination of international and national frameworks applicable to the non-living components and products of synthetic biology by this forum, therefore no conclusions can be drawn on whether or not these include socio-economic considerations, or whether these are even relevant or appropriate in the context. We therefore disagree with the assertion in paragraph 61 that socio-economic considerations are not sufficiently addressed by existing frameworks.

Para 52 (and para 31)

The illustrative examples of "potential benefits" and "potential adverse effects" differ in that specific examples and context are provided for the benefits, but the adverse effects are more general, for example how will there be an "increased level of toxic substances", or negative effects on pollinators? The AHTEG appears to have overlooked realities of synthetic biology that were raised in the online discussion, such as many applications being restricted to contained use, and that for an organism to have an impact it must be able to survive and reproduce in the natural environment (e.g. paragraph 55(a), UNEP/CBD/SYNBIO/AHTEG/2015/1/2). As stated several times above, considerations of the impacts of synthetic biology should be evidence-based and not speculative.

In regard to the listed potential adverse effects:

- (f): "changes in organisms on the level of basic metabolic pathways, such as altered photosynthesis pathways, carbohydrate metabolisms or nitrogen fixation" is stated to lead to changes in agricultural practices and this is presented as a potential adverse effect. However, such changes may well be a desired outcome in order to preserve biological diversity. In addition, it is stated that this "may challenge risk assessment" which is, in itself, not an objective of the conservation of biological diversity, and thus the statement is inappropriate and out of context.
- (k): the "loss of market share and income" due to "altered exploitation of genetic resources" is not a correct interpretation of the CBD objective of equitable sharing of benefits. Market

displacement due to substitution of the cultivated product for the synthetic biology product is evidently the underlying concern, and maintaining a market for a cultivated product is not necessarily consistent with or relevant to the three objectives of the CBD.

- (l) and (m): see comments for paragraph 31 above.
- (n): while these approaches (data protection versus sharing, as referred to in the comments above for paragraph 31) may have "different implications" in regard to access and benefit sharing, these require explanation of how they will have potentially adverse effects to be included in this list.

Para 57 and 65

We do not agree with the implication that frameworks for synthetic biology covering the living organisms and non-living components and products are needed in order for there to be comprehensive regulation of these in a way that is consistent with the objectives of the CBD. As stated above, the Cartagena Protocol provides the framework for living organisms (LMOs) created by synthetic biology (consistent with CDB art 8(g), as referred to in para 57), and we agree with the statements of paragraph 58 that this is a comprehensive framework which can be applied on a case-by-case basis to the specific circumstances. Paragraph 57 also cites decision XII/24 and falsely implies that this calls for a comprehensive synthetic biology framework. Further, there can be no conclusion that there is no comprehensive framework covering the living organisms and non-living products and components in the absence of an examination of the applicable frameworks outside the regime of the CBD and its Protocols.

We also do not consider it necessary that one comprehensive framework should apply to synthetic biology, which has broad application and the potential to span many sectors, and the fact that the frameworks are separated into different sectors does not lead to the conclusion that they are "fragmented" (paragraph 40). On the one hand, a single framework for synthetic biology is unlikely to be comprehensive enough, and on the other, such a framework will duplicate many others that have already long-existed. It is evident that assertions that a single comprehensive framework is needed for synthetic biology is aimed at expanding Parties obligations beyond that which they intended and have agreed to under the existing frameworks.

Para 66

For subparagraph (b), as we have stated for paragraph 34, we believe that these organisms are LMOs rather than "similar to".

For subparagraph (j), as we have also stated above, we disagree with the statement that there are gaps in oversight with regard to products and components of synthetic biology.

In addition, the definition still seems far from 'operational'. For instance, it is unclear how operational protocols can be established to regulate 'accelerating the understanding' of an organism.

UNEP/CBD/SYNBIO/AHTEG/2015/1/2

Para 13, 24, 25a

Synthetic biology is an approach rather than a technique, as it encompasses multiple disciplines from which tools and techniques may be applied for various purposes and end products and it is a continuum of modern biotechnology.

Para 15: Introduces a biased representation on the opinions expressed in the forum. As it reads at the moment, emphasis is placed on the views of a single on-line forum participant that expressed opinions about the relationship of synthetic biology and profit making which are not shared by the majority of the forum participants. Emphasising this single opinion in the report seems very biased.

Para 17 and Para 18 – There is a bias in the reporting of the opinions expressed in the on-line forum by focusing on the speculative position expressed by only few participants that " the increase of complexity and range of synthetic biology tools ….. need of stricter measures to prevent damage to biodiversity". During the forum discussions, many posts underlined the potential for higher predictability of outcomes and that a case-by-case risk assessment would address the above mentioned concerns. We recommend that this is reflected in these two paragraphs.

There appears to be an assumption that synthetic biology increases the "uncertainty" (as well as the number of potential "data gaps" in the risk assessment). This assumption is not necessarily correct but rather is driven because this is a "new technology". There is nothing inherent in synthetic biology that would necessarily increase the uncertainty; a well-designed synthetic system may have less uncertainty than some of the current untargeted methodologies.

Para 19

We disagree that process is a useful predictor of potential risk, harm or exposure. Process can be used to designate products that may possibly require additional evaluation, but it is only the output from the process that is important in the risk assessment. The current wording might be interpreted to mean that the process ("Synthetic Biology") is automatically equivalent to risk, harm, or exposure. We would like to emphasise the point made in paragraph 21 that there is no agreement amongst CBD Parties that synthetic biology is in fact a new and emerging issue, particularly in the context of

the three CBD objectives. As we have stated above, synthetic biology is a continuum of modern biotechnology with the living organisms created comprehensively regulated by the CBD and its Protocols, and the approach of separating synthetic biology into living organisms, and non-living components and products which are regulated under other frameworks does not make synthetic biology an emerging issue or create a need for a synthetic biology framework.

Paragraph 21: we recommend the words "synthetic organisms" to be replaced by "organisms developed with the use of synthetic biology approaches"

Para 43

We are also concerned with the list of "examples" of best practice provided in paragraph 43. These include the Guidance on Risk Assessment of Living Modified Organisms and the Training Manual on Risk Assessment of Living Modified Organisms, both of which have not been endorsed or adopted by the Parties to the Cartagena Protocol and thus cannot be seen as best practice. Further, the ETC Group is not an organisation with relevant direct experience or authority in relation to risk assessment and monitoring of LMOs. Ideally, for something to be a "best practice" it should have been tested, and assessed against alternatives and generally accepted by experienced practitioners as best practice.

Para 26(c)

"The production of living organisms through modern biotechnology and synthetic biology is similar but the genes and nucleic acid molecules transferred into the recipient organisms differ in that nucleic acids **transferred through modern biotechnology exist in nature *but not* those transferred through synthetic biology**. Therefore, some techniques of synthetic biology may or may not be readily classified as "*in vitro* nucleic acid techniques".

This statement has no scientific merit. Since the dawn of "modern biotechnology" genes have been chemically synthesized especially for the purpose of host codon usage. For instance, even recombinant human insulin was a synthetic gene that does not exist in nature. It is therefore incorrect to portray old molecular techniques as a form of 'cutting and pasting' naturally occurring genes between organisms and synthetic biology as an approach in which genes, not existing in nature, are chemically synthesized.

Para 26.d.

We recommend that the words "…may be completely different…" be replaced with the words "…may be fundamentally different…." The "fundamentally different" words are used later in the document. It is highly unlikely that most organisms produced using synthetic biology will be "completely different" – they may likely have DNA, RNA, proteins, etc. just like other organisms.

Para 28

The last sentence fragment, as well as by nonliving products and components (these are defined in Para 32). This implicates all three 'categories' (LMOs, nonliving, and products) as touching conservation, sustainable use and ABS. Para 32 *excludes* nonliving and products from Cartagena. Para 38 reflects on this exclusion, remediating that exclusion could bring all manner of fermentation derived chemicals and nonliving extracts, etc, under new review space.

Para 38.

Last sentence to rephrase from "The identified risks include the following" to "The potential risks may include the following". Many of the suggestions listed below that statement are hypothetical.

Para 48

There is no consensus that gene editing should be automatically considered "synthetic biology". For example, point mutation can be made in a single gene using gene editing tools similar to what can result from natural genetic diversity or conventional mutagenesis. This example is yet another testament how a mere use of a certain technique cannot be a pre-determinant of the feature ("synthetic" or not) of the outcome. Categorization of gene editing as "synthetic biology" automatically implies the resulted organism is an LMO - which contradicts the factually correct statement about currently undetermined regulatory (LMO) status (1st sentence). Additionally, 1st sentence reads as a biased opinion that it would be an "issue" if certain gene editing outcomes would NOT be considered LMOs. The lack of understanding on certain points might also be linked to different interpretations of certain scientific terms by different people.

We therefore recommend modifying para 48 the following way:

"On the other hand, some products produced by techniques such as gene editing, protocells and orthogonal systems may or may not be considered LMOs as per the definitions in the Cartagena Protocol and/or in national legislations. In this context, some submissions pointed to the need to clarifying the language of the Cartagena Protocol and/or national legislations with a view to making them fully adequate in addressing a broad range of current and future living organisms, while others were of the view that the development of a dedicated regulatory instrument which focused specifically on synthetic biology is necessary to fully address the three objectives of the Convention. Multiple commenters indicated that the current framework still fits for the needs."

Para 53

We believe that while the "methodologies" may need to be revised and adapted, the "principles" are unlikely to change.

Para 54

While there may be a potential for possible novel risks, we believe that a "revised risk assessment framework" is not needed. Modifications to methodologies may likely be needed.

Para 55.e.

It is unclear why the "…impacts on traditional practices and traditional knowledge … are usually not measurable." Certainly they can be measured. It is, however, very difficult to measure the impacts and even more difficult to place a value on the impact.

Para 57.c.

We believe that it would be more appropriate to word the first sentence as "In order to maximize potential benefits and avoid risks, and given the potentially high level of uncertainty…" We believe that it is inappropriate to assume that all use of new technology automatically results in increased uncertainty.