**TEMPLATE FOR PEER REVIEW COMMENTS**

**TECHNICAL SERIES ON SYNTHETIC BIOLOGY**

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| **Comments on the Technical Series on Synthetic Biology** |
| **Page #** | **Line #** | **Comment** |
| General Comment | The broad working definition of synthetic biology adopted by the CBD creates a difficulty for this document, since there are examples of synthetic biology mentioned herein that are inappropriate, since they would be products of methods that predate LMOs. Therefore, this document illustrates the lack of clarity regarding the term that underpins all the current discussions of synthetic biology under the CBD. |
| General Comment | As a related comment, the confusion about whether synthetic biology is a single discipline, which it is not in this reviewer’s opinion, or a collection (yet to be defined) of disciplines pervades this document. |
| General Comment | The status of certain projects mentioned in this document should be re-evaluated, since, for example, characterizing gene drive containing solutions for public health as in advanced development is inaccurate. |
| 8 | 8 | Regarding the term “potential risk” used here and throughout the document: the concept of potential (i.e. possible) is already incorporated in the definition of risk. Thus potential risk is simply risk. The terminology should be adjusted accordingly. |
| 8 | 21 | Throughout the document: substitute the word “discipline” with "category". "Discipline" implies an organized or recognizable area of endeavor, but since the definition of Synthetic Biology is still under discussion even under the CBD, with only a working definition agreed upon for the purpose of facilitating discussion, Synthetic Biology cannot be considered a discipline for the purposes of this document. Page 9, lines 21 and 22 also supports the lack of consensus on what Synthetic Biology is, and therefore the lack of what would constitute a discipline. On page 10, lines 14-20, a long list of technologies and tools that are described to be within the scope of synthetic biology is given. The items in the list are referred to as disciplines. Those lines contradict the statement here that refers to synthetic biology as a single discipline. Therefore, while the statement that synthetic biology is often referred to as a single discipline might be true, it is important to state that synthetic biology is not a single discipline. |
| 8 | 47 | “...appear ill-equipped…” is not a conclusion that can be made, nor within the scope of this document. |
| 10 | 1 | It should also be noted that there is significant effort developing synthetic biology applications that are not expected to have market value, but will be deployed in a not-for-profit way. These might not have a market value but will contribute significantly to economic productivity through the expected health benefits. |
| 10 | 47 | Define the use of the word "market". The gene drive applications currently under development are not going to be commercially distributed. In particular, the gene drive applications listed in Table 1, for the control of vector-borne diseases, will not be marketed, but will be deployed by governments or regional bodies as part of a public health campaign. Furthermore, the status of the gene drive research should not be classified as in the advanced stages. There have been no field trials of such synthetic biology developments, and therefore they are quite early in the developmental pathway. |
| 11 | 5 | Replace “largely” with "entirely". No data are so far available on the impacts of these applications on the conservation and sustainable use of biodiversity. If the authors are aware of any studies, they should be reviewed in this document, since they would be key examples to note, and then “largely” can be used. |
| 11 | 7 | In the same vein as the previous comment, this should be "entirely"? |
| 11 | 12 | This section does not describe any experience, and therefore should not be titled as such. The discussion here lays out more nuanced speculations, not experiences. |
| 12 | 23 | Delete this sentence fragment. |
| 12 | 34-38 | This is a key statement. To date, the application of a precautionary approach has tended to discount any benefits in the risk assessment and decision-making equation. These sentences signal that a re-interpretation of the precautionary approach might be necessary. Please consider stating this more explicitly in the document. |
| 12 | 49 | This statement reverts to the first view of synthetic biology as a single discipline. Clarity is needed in this regard. It is not simply a matter of semantics; it indicates a perspective on the way regulations are developed |
| 13 | 22 | See previous comments on synthetic biology as a single discipline. |
| 13 | 31 | Refer to Entine J, Felipe MSS, Groenewald J-H, et al (2021) Regulatory approaches for genome edited agricultural plants in select countries and jurisdictions around the world. Transgenic Research. https://doi.org/10.1007/s11248-021-00257-8 |
| 15 | 32-33 | Here, the document seems to take a skeptical view of the term "synthetic biology" because of the lack of a clearly established agreement on what that term encompasses. Therefore, it cannot be a single discipline. |
| 16 | 23 | Commercialisation has to be defined, since some important applications of synthetic biology will not be distributed through a commercial enterprise. |
| 18 | 9 | Random mutagenesis is a traditional tool. Selection of random mutants would be out of scope of the Cartagena Protocol, but as mentioned in 8.1.4(a) is in the scope of the CBD. |
| 19 | 27-28 | It is improper to refer to the patterns of inheritance observed by Mendel as laws. They are one pattern of inheritance that has been observed, but in fact there are other patterns of inheritance that occur in nature, and referring to these as aberrant is a value judgment that cannot be imposed. That perspective leads to the inference that these non-Mendelian patterns are more risky. **That inference has yet to find scientific support and therefore has to be avoided when considering gene drives.** See these references that describe the prevalence of non-Mendelian inheritance patterns in nature.Hurst, L. D., 2019 A century of bias in genetics and evolution. Heredity 123: 33-43.10.1038/s41437-019-0194-2Fishman, L., and M. McIntosh, 2019 Standard deviations: The biological bases of transmission ratio distortion. Annual Review of Genetics 53: 347-372.10.1146/annurev-genet-112618-043905Seymour, D. K. C., E.; Arioz, B. I.; Koenig, D.; Weigel, D., 2019 Transmission ratio distortion is frequent in *Arabidopsis thaliana* controlled crosses. Heredity 122: 294-304.10.1038/s41437-018-0107-9Zollner, S. W., X. Q.; Hanchard, N. A.; Herbert, M. A.; Ober, C.; Pritchard, J. K., 2004 Evidence for extensive transmission distortion in the human genome. American Journal of Human Genetics 74: 62-72.10.1086/381131 |
| 19 | 33-34 | Good point! This should be emphasized throughout. |
| 19 | 38 | An increase in gene frequency can be the result of other mechanisms, not just a result of gene drive. For example, natural selection also increases the frequency of an allele. That point should be made here. |
| 32 | 20 | This section should also reference newer Oxitec technology. The self-limiting technology still constitutes a bio-contained system because the transgenics do not survive after a few generations. |
| 41 | 13 | See my previous comments on this concept. |
| 41 | 25 | This reinforces the idea introduced on p. 12, lines 34-38 of including benefits in the assessment of impacts when deciding on the deployment of a technology, and not merely a precautionary approach based on risk considerations only. |
| 42 | 18-19 | This phrase is confusing, since the subject of this section is Invasive Alien Species. It should be deleted. |
| 42 | 20-23 | These speculated impacts are case specific, and are not applicable to all gene edited organisms. |
| 43 | 7-8 | A relevant publication here is Collins, C. M., J. A. S. Bonds, M. M. Quinlan, and J. D. Mumford. “Effects of the Removal or Reduction in Density of the Malaria Mosquito, *Anopheles gambiae* s.l., on Interacting Predators and Competitors in Local Ecosystems.” Medical and Veterinary Entomology 33, no. 1 (March 2019): 1–15. https://doi.org/10.1111/mve.12327. |
| 43 | 15-20 | These are not structurally different types of drive. Their effect (either suppression or replacement) depends upon the effector gene contained within the drive construct. |
| 43 | 22-23 | Replacement drives have the goal of keeping the target population at the same levels but changing their characteristics so that they are no longer harmful, such as *An. gambiae* that can no longer serve as *Plasmodium* hosts. Thus these two different types of drive do not have this goal in common. |
| 43 | 23 |  For example, risk assessment should consider the possibility that... |
| 43 | 43-45 |  Research to overcome resistance should be mentioned as well. |
| 44 | 3 | Lower numbers are not the expected result of replacement drives. |
| 44 | 17 | Likelihood of invasiveness is a consequence of the design of the drive. Therefore, this is not a statement that can be made generally for gene drives, despite the opinions expressed in the sources cited. Some gene drives will be designed to not be self-sustaining. |
| 44 | 19 | However, spread would be limited by geographic distribution of target species, since the presence of the species is required for the gene drive construct to spread. |
| 44 | 31 | Many regulatory regimes would not regulate these as GMOs/LMOs. In fact, it is questionable whether these should be cited as examples of synthetic biology altogether. |
| 48 | 8 | This section seems quite judgmental, emphasizing the need to consult society as a whole rather than those elements of society that are most likely to be affected by the technology. This is counter to the common thinking that the opinions of those who will be most impacted should be prioritized. |
| 48 | 23 | This document should also consider adding in this section a comment about the ethical obligation not to disseminate misinformation in the context of "informed consultations" |
| 48 | 24-25 | These stakeholder consultations should consider local populations' view of benefits as well as risks, consistent with what is said previously in these comments (see comments to p.12, lines 34-38; and p. 41, line 25). |
| 49 | 1 | This statement further supports a risk and benefits consideration when assessing the impacts of the technologies mentioned in the document and subsequently deciding to approve or deny it. |
| 52 | 5-6 | The WHO (2021) perspective should be included here, as in this quote:“It is important to avoid processes that privilege some communities over others, leading to procedural injustice and inequity. The key message for researchers is that efforts should be made to ensure that communities, stakeholdersand publics are appropriately engaged, and that host communities for GMM release are given the opportunity to provide legitimate authorization for the release.  |
| 58 | 11 | However, there are useful risk assessment paradigms that could be mentioned here, such as the regulation of bio-control agents. |
| 58 | 23 | The references proposing that existing risk assessment methodologies may be applicable should be listed rather than given this superficial acknowledgment. There is no recognition that there is a legitimate difference of opinion on this point. |
| 58 | 38-39 | Suggested rewrite: change “ limited intime and space and therefore provide data from small-scale tests that can be relevant to large-scale releases,” to “...confined in time and space during small-scale tests, which allows the generation of data in those tests that can be relevant to large-scale releases,” |
| 59 | 7-8 | This concern is addressed during the standard crop development process, since deleterious effects of off-target editing would normally be detected during the development and testing process, and during the generation of field data for agronomic characterization and food safety evaluations consistent with the guidelines of the Codex Alimentarius. (Codex Alimentarius - Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants. FAO/WHO, 2003.) Therefore, this issue is no different from current LMO plants. Furthermore, research in ongoing that increases specificity of the nuclease used in editing. |
| 60 | 11-12 | This statement is incorrect. Plants using RNAi have been commercialized from the beginning of GMO crop development. In fact the first GMO plant product, Flavr Savr, was an example of RNAi technology (Krieger, Elysia K., Edwards Allen, Larry A. Gilbertson, James K. Roberts, William Hiatt, and Rick A. Sanders. “The Flavr Savr Tomato, an Early Example of RNAi Technology.” HortScience 43, no. 3 (June 2008): 962–64. <https://doi.org/10.21273/HORTSCI.43.3.962>). Therefore, there are already risk assessment examples of RNAi, and RNAi GM crops are already among the commercialized suite of crops. Another early example is virus resistant papaya (Azad, Md. Abul Kalam, Latifah Amin, and Nik Marzuki Sidik. “Gene Technology for Papaya Ringspot Virus Disease Management.” Edited by S. Rodtong and R. Dinkins. The Scientific World Journal 2014 (March 17, 2014): 768038. https://doi.org/10.1155/2014/768038). A recent example is the INNATE potato product of Simplot (<https://www.simplot.com/news/innate_potato_receives_fda_safety_clearance>). |
| 62 | 21 | This section misses discussing strategies to limit spread via split or multi-component drives, which are biocontainment approaches, as opposed to the others described in this section and the next, which are designed to reverse a drive. |
| 63 | 31 | There is no clear distinction between the mitigation strategies described in this section and those described in the previous section, since some examples in the previous section also act to reverse a drive that has already been released. |
| 67 | 44-46 | Since gene drive organisms are already currently under the CBD and its Protocols, this statement implies that there is an alternative being advanced or considered. Such alternatives should be described here if they exist, or if not, then this statement seems superfluous and possibly misleading in its implications. |
| 71 | 13 | These other perspectives should be referenced and not simply mentioned casually. |
| 73 | 4 | This phrase, “appear to be valid concerns”, interjects a value judgment on those concerns, which are inappropriate for this document. I suggest that the document be screened for similar value judgments, which should be eliminated. |
| 73 | 17-18 | Engineered gene drives are not approaching commercial release. |
| 76 | 41-42 | These are not “near-market ready”, if this phrase has the meaning that I think it does. |
| 83 | 20-21 | Conversely, neither would a modification that resulted from the use of modern biotechnology that was not a novel combination. Thus some results of gene editing would not be considered an LMO under the Cartagena Protocol, nor should it be the subject of further regulations even if they could be made to fit in the category of synthetic biology (depending upon how that term is ultimately defined). |
| 85 | 4-5 | It would be instructive to survey Parties to determine whether any of them regulate naked DNA and parts as "living modified organisms". The word “may” in this sentence should probably change to “do”. |
| 85 | 11 | Pursuant to my previous comment, do any countries do so? If not, this sentence should read “all countries” rather than “many countries”. |
| 87 | 38-40 | This sentence will now have to be revised. |
| 90 | 1-5 | The meaning of these sentences is unclear. Are there no international bodies that address pharmaceuticals? Currently recombinant DNA-based vaccines (such as those used by Johnson and Johnson or AstraZeneca to develop COVID19 vaccines) are not within the scope of the Cartagena Protocol as far as I know. |
| 93 | 20 | The example is described in 3.3.1(d) rather than Section 3.2? |
| 96 | 4 | This section is missing two key WHO documents, both mentioning gene drives, with the 2021 edition updated to take into account developments in the area of gene drive research:World Health Organization. Guidance Framework for Testing of Genetically Modified Mosquitoes. Geneva: World Health Organization, 2014.World Health Organization. Guidance Framework for Testing Genetically Modified Mosquitoes, Second Edition. Geneva: World Health Organization, 2021. |
| 100 | 3-14 | Redundancies in these two paragraphs need to be resolved. |
| 121 | 31-33 | This sentence needs to be rewritten to be fully understandable. |
| 125 | 38 | Delete the letter l. |
| 128 | 8-9 | However, the WHO would not allow or prohibit synthetic biology products per se; but rather would recommend whether a product could be used, based on its review that would include safety and efficacy considerations. Guidance documents issued by the WHO describe those considerations. |
| 131 | 23 | The acronym should be FPIC. |
| 133 | 14 | Also add the Genetic Engineering and Society Center at North Carolina State University (https://research.ncsu.edu/ges) |
| 132 | 8 | Engineered gene drives provide a useful lens through which to evaluate overlaps and potential gaps only to the extent that the research and development of these organisms has progressed. Gene drives have not progressed very far down the development pathway. |
| 132 | 23 | See above comment to p. 96, line 4 for the references to these guidance documents. |
| 132 | 31 | However, measures to control disease vectors by means such as pesticides, and generally human intervention in nature, including the development of agriculture, are interventions in nature that cannot be avoided. |
| 133 | 9-10 | Not in advanced development. |
| 134 | 3-4 | References to this work should be provided. |
| 134 | 22 | change “form” to “from” |

Please submit your comments to secretariat@cbd.int.