**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** |
| 8 | 5 | Synthetic biology is not one discipline, it rather includes a combination of disciplines (mol. biology, engineering, biophysics and many others) |
| 8 | 8 | As it stands this statement sounds as if this is some unique risk associated with these modern technologies. It is not. Other conventional interventions such as pesticides can have a great impact on biodiversity. Also, there are synthetic biology approaches that are aimed at conservation and restoring biodiversity (e.g. against invasive species in Australia), therefore it is not precise to put them all under the generic umbrella of causing a potential risk to biodiversity. |
| 8 | 15-16 | “Can be applied” as “tool to spread through a population”. This implies that these engineered gene drives are ready to be released, which is not the case.All experiments and results so far have been obtained from contained lab populations.  |
| 10 | 4 | There are many not-for profit research projects that develop engineered gene drives to provide potential solutions to challenges regarding public health and conservation. |
| 10 | 10-17 | This complexity of areas suggests it is not one single discipline. |
| 10 | 47 | Current engineered gene drives in development are not for profit and will not be commercially sold.  |
| 11 | 5 | If it is largely hypothetical there should be examples listed which application has affected biodiversity.  |
| 11 | 23 | Sentence incomplete |
| 12 | 34 | Indeed, so far risk assessments under the precautionary principle tend to not include benefits. |
| 13 | 1 | Again here it is stated “the potential impacts of synthetic biology” is referring to one single discipline. However, since it involves such a wide technical area is, it is more likely that different synthetic biology technologies may have very different impacts.  |
| 13 | 40 | In Table 1 Engineered gene drives in mosquitoes for control of vectorborne diseases and Engineered gene drive for an agricultural pest are listed in the advanced stage. All of these gene drives are still under research and development. There have been no field trials and all results so far are based on experiments done in laboratory populations. Therefore, these examples fall still under the research stage. |
| 17 | 21 | The focus is very much on commercial value, however some of those technologies are also developed to improve public health and conservation, which will not be distributed commercially. |
| 19 | 27-28 | Gene Drive is not a phenomenon and that is not how it is worded in the reference that is cited. As stated in the next sentence, there are many natural gene drive systems which can favour their own inheritance. |
| 19 | 38 | Natural selection also favours inheritance of certain traits |
| 19 | 43 | It should be stated that the gene drive will produce offspring that “potentially” all carry the gene drive, as often the homing rate is not 100% due to non-homologous end-joining (NHEJ). |
| 32 | 11 | Target Malaria has not done any field trials with gene drive mosquitoes. All gene drive strains are still under development and assessment in a contained facility. Therefore the following sentence “Similar initiatives are also underway but in contained conditions.” Should be deleted. |
| 32 | 20-33 | It might be good to reference Oxitec here |
| 40 | 27-29 | How is the advanced stage of development defined? All of the gene drive constructs to potentially control vector populations are still under research and development. There have been no field trials and more experiments are needed to assess these strains and other potential gene drive candidates. |
| 41 | 13-15 | Which is why it should not be regarded as single discipline |
| 41 | 25 | As phrased in the previous sentence, there are benefits associated with these applications. These should be considered when assessing the potential impact of the application on a case by case basis. |
| 41 | 45 | The gene drive applications under development for vector control will not be commercially distributed. The technology will be shared and will be deployed by government authorities or regional governing bodies with the aim to improve public health. |
| 42 | 1-2 | Which is again why benefits should be included in a case-by case risk assessment. |
| 42 | 17-20 | These events are all hypothetical, and their relevance is construct specific.  |
| 42 | 31-33 | This statement cannot be generalised as it is. The major advantage of a gene drive over conventional interventions against disease vectors is that it can spread and affect areas that cannot be easily assessed with existing vector control measures. |
| 42 | 36-37 | There are other interventions such as the widespread use of bednets and IRS that reduce mosquito populations and could have an impact on ecosystems. That risk is not unique to gene drives. |
| 42 | 44-46 | That risk is construct and species dependent (how closely are species related to eachother and are they able to form fertile hybrids). |
| 43 | 4 | There is a study by Collins et al which addressed this. Collins CM, Bonds JAS, Quinlan MM, Mumford JD. Effects of the removal or reduction in density of the malaria mosquito, Anopheles gambiae s.l., on interacting predators and competitors in local ecosystems. Med Vet Entomol. 2019 Mar;33(1):1-15. doi: 10.1111/mve.12327. Epub 2018 Jul 25. PMID: 30044507; PMCID: PMC6378608. |
| 43 | 24 | It would be more precise to state “suppression” or “reduction” drive as stated in line 15. |
| 43 | 24-26 | That distinction is not correct. A replacement drive could affect non-target species e.g. via hybridisation. Likewise, a suppression drive could potentially alter the target species in an unintended manner (e.g. through an off-target effect that makes mosquitoes more resistant to insecticides, if this is coupled with low effectiveness of the suppression this could pose a potential harm). |
| 43 | 33 | This statement needs a reference. Further it is stated that resistance is important (?). It is rather an important concern. |
| 43 | 36 | Resistances to target sites are not a phenomena (as is known for insecticides). Add reference. |
| 43 | 40 | Please add a reference. |
| 43 | 44-45 | “It is rather uncertain how rapidly it spreads” What does this sentence imply? This does not constitute a potential harm. |
| 44 | 3 | Lower numbers are not expected for mosquito replacement strategies. |
| 44 | 2-10 | This does not consider the potential application of population suppression gene drives to alien species. Also, again the potential reduction in vector numbers is not unique for population suppression gene drives. This has been achieved through other vector control interventions (e.g. insecticides) as well. |
| 44 | 16-20 | As mentioned in the sentence about variation persistence before, the level of invasiveness depends on the construct and application and cannot be generalised for all gene drives. |
| 44 | 22 | Not all gene drive will affect food security. |
| 44 | 21 | Replace “can” with “could” as that is speculative |
| 44 | 23 | Mitigate harm, implies that by default there is a harm to humans or the environment from using gene drives |
| 45 | 6-7 | Comparing off-targets from conventional breeding to modern breeding technologies actually shows that off-targets are much lower in newer technologies. Singer, Stacy & Laurie, John & Bilichak, Andriy & Kumar, Santosh & Singh, Jaswinder. (2021). Genetic Variation and Unintended Risk in the Context of Old and New Breeding Techniques. Critical Reviews in Plant Sciences. 40. 1-41. 10.1080/07352689.2021.1883826. |
| 48 | 22-24 | This consultation should include views on risks as well as benefits from these communities |
| 48 | 29-34 | Applications should be published in advance of construction of any synthetic biology technology? Is that requirement and generalisation proportional to other technologies? These technologies are developed in containment laboratories and are not released without permission. |
| 48 | 39 | Should there not be a priority on those most affected by the specific application. How different are protection goals between different communities? |
| 48 | 44 | See comment above. Not everyone will be affected by these applications. Therefore, the view of those most affected by the application should be prioritised. |
| 48 | 46 | The extend to which that harm be acceptable and consideration of the benefits the technology might provide. |
| 49 | 1 | Yes, this would involve rather a risk-benefit analysis then just a risk assessment |
| 53 | 35-40 | Again, this concern is not specific to synthetic biology technologies. Common breeding techniques are not natural. |
| 53 | 48-50 | The messaging of that sentence is not clear. It is not by default that this technology causes harm. |
| 56 | 39-40 | They are also product specific. |
| 58 | 11-12 | This is very generic. There will be uncertainties, however, it remains to be assessed on a case-by-case basis if those uncertainties are acceptable or not.There are risk assessments for biological control agents which could be mentioned here. |
| 58 | 15-18 | This requires a reference |
| 58 | 29 | Lack of experience and capacity – who does this refer to? |
| 58 | 33-35 | That depends on the construct and the released environment |
| 58 | 38-41 | Self-limiting gene drives that are spatially and temporally limited are in development (e.g. daisy chains, split drives). Noble C, Min J, Olejarz J, Buchthal J, Chavez A, Smidler AL, DeBenedictis EA, Church GM, Nowak MA, Esvelt KM. Daisy-chain gene drives for the alteration of local populations. Proc Natl Acad Sci U S A. 2019 Apr 23;116(17):8275-8282. doi: 10.1073/pnas.1716358116. Epub 2019 Apr 2. PMID: 30940750; PMCID: PMC6486765. |
| 58 | 42-43 | There is no engineered gene drive that is close to a potential release. Any Gene drives developed which show promise to achieve for example population suppression base don laboratory experiments are still under research and development. |
| 62 | 31-40 | The use of localised high threshold (underdominance) and self-limiting drives (split drives, daisy chains and killer rescue ) is missing.  |
| 63 | 35 | These examples (e.g. daisy chains, underdominance) do not fall under the title for this section (post release removal) |
| 67 | 20-21 | Please replace “most are not ready” with “none are ready” for release |
| 67 | 24-25 | These gene drives are undergoing a thorough assessment which is driven by the developers. That is why these gene drives are still in the research and development phase and not close to any release as stated in previous sections. |
| 88 | 23 | That may be case specific, but not generic to all synthetic biology techniques |
| 106 | 11-12 | Reference Alphey et al., 2020. Alphey LS, Crisanti A, Randazzo FF, Akbari OS. Opinion: Standardizing the definition of gene drive. *Proc Natl Acad Sci U S A*. 2020;117(49):30864-30867. doi:10.1073/pnas.2020417117 |
| 106 | 14-15 | Importantly, these released self-limiting engineered insects do not contain gene drive constructs. |
| 132 | 8 | Again, engineered gene drives are not close to release. |
| 132 | 31-32 | Current interventions e.g. use of insecticides are already intervening in nature but are needed for control of vector borne diseases. |
| 132 | 31-35 | How does this consideration compare to current interventions? |
| 133 | 9-10 | Again, engineered gene drives are still in the research and development phase and not close to potential release |
| 134 | 31-32 | Which is case specific and cannot be generalised |

Please submit your comments to secretariat@cbd.int.