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| **Comments on the Technical Series on Synthetic Biology** |
| **Page #** | **Line #** | **Comment** |
| 0 | General Comment 1 | Goes beyond the available evidence of the alleged benefits of Synthetic Biology (also called Synbio) while under-emphazising the risks to an extent that is misleading when read overall. Passages are phrased in a way that implies benefits are likely, underplaying the high level of uncertainty that surround many applications of Synbio. Assumes future environments will inevitably include Synbio applications, even though the need for Synbio has still not been demonstrated. |
| 0 | General Comment2 | Fails to mention viable alternative solutions to the problems that are supposed to be addressed with Synthetic Biology applications, thus giving the impression that Synbio is the only option. It disregards other pathways, such as those based on the affirmation of food sovereignty through community, small holders and Indigenous Knowledge systems |
| 0 | General Comment3 | Only makes one mention of the fact that issues of risk inherent in Synbio technologies cannot be dealt with by science alone. Does not explore the social and ecological aspects of the risks that are inherent in Synbio. These include: promoting artificiality and more uniformity in food crops and systems, more monoculture plantations which negatively impact biodiversity, the use of bio-vats instead of natural production, higher energy usage, higher dependency on proprietary seeds, organisms and applications. |
| 0 | General Comment4 | Recognises the need for assessment based on economic, political, moral and ethical concerns, but says this will have to be case-by-case, rather than looking at the area as a whole in order to establish a global assessment framework and not allow a fragmented and incoherent evaluation to happen in each case and each place. This is non-sensical as it assumes that there will not be risks that are generic, as there are in conventional GMOs and LMOs, for example. |
| 0 | General Comment5 | Refers to Free Prior and Informed Consent (FPIC), but fails to acknowledge the fundamental difference between current engagement processes, undertaken by those developing the technology (leading to a conflict of interest), and the principles of FPIC which underlie genuinely participatory processes of technology assessment. This conflict of interest must be acknowledged in the report. An honest FPIC process would not be commissioned by the technology’s promoters and others who stand to profit of the technologies, but instead by a wide range of rights-holders, including Indigenous peoples and local communities. |
|  8 | 13 | The listed benefits in agriculture are speculative and dependent on which farming system is used (i.e. not the one used by the majority of small holders / peasants in the world). Yet these benefits are stated as fact. |
| 8 | 25 | Ignores known risks that are built into the very design of many Synbio applications (e.g. risk of grave loss of biodiversity through engineered gene drives). Instead of calling for the assessment of these risks to take place in the phase where technologies are still being conceptualised and/or developed, the paper states that only case-by-case risk assessment might be enough, implying this could happen after they have already been developed.  |
| 8 | 26 and elsewhere | The use of “science-based” in the context of assessment should be more thoroughly defined to acknowledge that what is referred to is just one specific methodology. Limiting assessment to one narrow ideological view point is not scientific in the normal sense of the word, but scientism. It is vital that the methodology of ‘science’ that will be used for assessments is not restricted to the dominant method being used by developers of synbio products, but is instead interdisciplinary, reflecting the totality of scientific knowledge across nations and territories that may be targeted for releases/commercialisation of future Synbio products. |
| 9 | 7 | It is good to calls for “integration with social sciences and engagement with communities”, but this should be implented in this document. Yet the paper only cites examples of this being undertaken by the proponents of the technology (see General Comment 4). |
| 18 | 42 | Says TALENS have a high degree of precision and control, but there is strong evidence from hornless cattle recently developed in the US, that this is not the case. They were later found to have accidental integrations of plasmid DNA, including antibiotic resistance genes (Norris et al., 2020 - <https://www.technologyreview.com/2019/08/29/65364/recombinetics-gene-edited-hornless-cattle-major-dna-screwup/>). It is vital that introductory text to technologies is accurate, and not based on unsubstantiated claims of utility or efficacy. Norris, A. L., Lee, S. S., Greenlees, K. J., Tadesse, D. A., Miller, M. F., & Lombardi, H. A. (2020). Template plasmid integration in germline genome-edited cattle. *Nature Biotechnology*, *38*(2), 163–164. https://doi.org/10.1038/s41587-019-0394-6 |
| 18 | 47 | Using the term “advances”, implies that applications have been made in the area of plant and animal engineering and health applications. The overwhelming majority of CRISPR use is still at the preliminary research stage without demonstrable ‘advances’ for commercialised products. It would therefore be more accurate to state that CRISPR-Cas systems have led to ‘preliminary research advances’ rather than |
| 31 | 27 | As written the statement implies that a company (Oxitec) has developed a self-limiting GM mosquito, when, in reality, this is still at the experimental stage, with several unpredicted effects reported and no benefits yet demonstrated. |
| 31 | 36 | The Menz (2020) study the paper cites itself suggests that the claims of those producing the cultivars have yet to be substantiated, yet the success of the technique is stated as fact. Given the information provided by Menz et al., (2020), the sentence should be corrected to reflect that traits improving yield, nutrition or pest resistance are in development e.g. the sentence could be modified to: “Menz et al., (2020) have recently reviewed and estimated that 140 genome-edited cultivars of 36 crops that aim to improve yields, nutrition, and pest resistance, are already under development, *though evidence of efficacy remains to be substantiated*.” |
| 41 | Entire section 4.1 | In discussing the positive and negative impacts of gene drives, potential negative impacts on disease epidemiology have not been included, both as a result of efficacy failures/ unintended effects (Beisel and Boëte, 2013; Sirinathsinghji et al., 2019). It is vital that gene drive technologies are not incorrectly and simplistically framed as having only potential benefits on disease, while potential negative effects are limited to ecological impacts.Potential adverse effects on health, such as disease resurgence in the event of drive resistance development and population re-bound are even acknowledged by gene drive developers (James et al., 2020), and also raised in the WHO guidance materials (2021). Niche-replacement with other disease vectors, the development of increased pathogenicity in response to effector molecules in gene replacement drives, increases in vector competence and capacity are also potential outcomes. Moreover, some of these adverse effects cannot be assessed prior to release. Wider ecological and social determinants are completely omitted, ranging from issues such as behavioural resistance; and impacts on wider social determinants of disease and existing treatments that may suffer opportunity costs from any narrow technological focus on disease interventions. Of note, China has been recently declared malaria free, based largely on access to free health services, surveillance and political coordination, demonstrating the importance of existing strategies in defeating vector borne disease. Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. <https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/>Beisel U and Boëte C (2013). The Flying Public Health Tool: Genetically Modified Mosquitoes and Malaria Control. *Science as Culture*, 22, 38-60. doi: 10.1080/09505431.2013.776364James, S. L., Marshall, J. M., Christophides, G. K., Okumu, F. O. & Nolan, T. Toward the Definition of Efficacy and Safety Criteria for Advancing Gene Drive-Modified Mosquitoes to Field Testing. *Vector-Borne Zoonotic Dis.* **20**, 237–251 (2020). |
| 42 | 47 | It is currently premature to state that gene drives offer “genuine potential” for continental-wide eradication. This wording should be corrected for bias. It is generally accepted that gene drives will not completely eliminate mosquitoes, and some modelling suggests that releases will result in heterogeneous populations of wild-type and gene drive mosquitoes, even with regular releases (e.g. North et al., 2020). More recent data suggests that various ecological and climactic factors may have significant impacts on efficacy that remains understudied (Morris et al., 2021). Other issues, such as drive resistance, may also impede efficacy. It remains scientifically premature to state that they offer “genuine potential” for eradication across a continent. We suggest the sentence is corrected to reflect the uncertainty of gene drive efficacy as follows: “This approach *is designed to* increase the feasibility of large-scale control, *though* potential for continental- scale eradication of unwanted wild populations or species *remains questionable, with potential for unintended effects such as drive resistance expected to impede eradication efforts.*” North, A.R., Burt, A. & Godfray, H.C.J. Modelling the suppression of a malaria vector using a CRISPR-Cas9 gene drive to reduce female fertility. *BMC Biol* **18,**98 (2020). <https://doi.org/10.1186/s12915-020-00834-z>Morris, A.L., Ghani, A. & Ferguson, N. Fine-scale estimation of key life-history parameters of malaria vectors: implications for next-generation vector control technologies. *Parasites Vectors* **14,**311 (2021). https://doi.org/10.1186/s13071-021-04789-0 |
| 42 | 29 | Island locations are not ecologically confined, and thus island releases also raise concerns regarding spread beyond site releases. The sentence erroneously conveys a notion that there is consensus regarding island locations being ‘appealing’ sites for release, when there is actually none. As recently acknowledged by the 2017 Synthetic Biology AHTEG: “Islands are not ecologically fully contained environments and should not be regarded as fulfilling the conditions in the definition of contained use as per Article 3 of the Cartagena Protocol unless it is so demonstrated.” |
| 46 | 37 | The paper notes considerable uncertainty, but does not explain the seriousness of the threat in a reasonable worst case scenario - i.e. that the use of Synbio could destabilise whole ecosystems, and potentially the global meteorological systems, with potentially devastating results. |
| 50 | 33 | Describes engagement processes initiated by proponents of Synbio, but ignores critiques of such engagement processes and the problem of ethics dumping in the Global South (Bassey-Orovwuje et al. 2019).Bassey-Orovwuje, M., Thomas, J. & Wakeford, T. Exterminator Genes: The Right to Say No to Ethics Dumping. Development 62, 121–127 (2019). https://doi.org/10.1057/s41301-019-00214-3 |
| 50 | 35-43 | A clear distinction should be made between the engagement strategies from developers or proponents of a technology, such as highlighted in this section (e.g. Target Malaria) and genuine processes that aim to obtain the free, prior and informed consent (FPIC) of potentially affected communities. In the former, there could be potential conflicts of interests, and questions can be asked as to whether the consent that is sought is freely given without pressure or manipulation, and whether the information that is provided is unbiased and explains the risks adequately. |
| 52 | 44 | This is an inadequate discussion of the ethical and epistemological arguments about gene drives in the context of Indigenous people’s autonomy, cosmovisions and knowledge systems. The economic paradigm of ecosystems services (Line 49) is just one methodology that people have devised to value biodiversity and is not considered appropriate by a wide range of Indigenous peoples and local communities (Goldtooth 2016).Goldtooth, T (2016). Judge’s Statement. Paris International Rights of Nature Tribunal. <https://www.therightsofnature.org/paris-financialization-of-nature/>  |
| 57 | 21 | We strongly support the statement that the acceptability of risk is a social construct (i.e. an issue to be decided through legitimate political processes) and thus must involve a wide range of non-scientific criteria along with scientific parameters as one in the list of needed evaluation criteria, that can be debated as part of processes of participatory democracy. Indigenous and community farmers knowledge systems should be part of the risk assessment criteria, as well as their right to FPIC. |
| 57 | 27-30 | This section could be strengthened to include the paper by Heinemann et al, (2021), which refers to the increasing scale of human interventions as a result of emerging technologies (e.g. dsRNAs, gene drives, genome editing), which is now becoming part of what could be considered genetic engineering of whole environments. The scale of such interventions can be considered to be a risk in itself, and a major concern when considering the rapid development of synbio technologies for environmental release. As highlighted by Heinemann et al. (2021), mutations introduced by genome editing or other genetic technologies are not reliant on the processes of evolution, but instead can be driven by human attempts to ensure such mutations establish and spread in the environment. Heinemann, J. A., Paull, D. J., Walker, S., & Kurenbach, B. (2021). Differentiated impacts of human interventions on nature. *Elementa: Science of the Anthropocene*, *9*(1), 00086. https://doi.org/10.1525/elementa.2021.00086 |
| 58 | 11-12 | An interlinked challenge for gene drive RA to the issue of spread and persistence being their *raison d’etre,* is the lack of ability to mitigate, recall or reverse a gene drive release, as acknowledged by the latest AHTEG on RA/RM. Any release can thus not currently be controlled, fundamentally challenging the validity of a phased-approach, or reversed in the event of a gene drive release going awry (Then 2020). This sentence should thus be strengthened to acknowledge this. Suggested addition: “*Combined with the lack of mitigation strategies for recalling or reversing gene drive releases, such issues warrant additional steps in ant risk assessment process that can operationalise the precautionary principle, including the introduction of cut-off criteria early in the process that can be applied when uncertainty is too high to ensure against adverse impacts.”* Then C. (2020) Limits of Knowledge and Tipping Points in the Risk Assessment of Gene Drive Organisms. In: von Gleich A., Schröder W. (eds) Gene Drives at Tipping Points. Springer, Cham. https://doi.org/10.1007/978-3-030-38934-5\_8 |
| 58 | 28 | We disagree that a lack of validated modelling tools is the issue *per se*, rather it’s that modelling can never be validated without empirical testing, which would require deployment or release into the environment. As such, it is a perverse situation where deployment would inform on the validity of a model, rather than the model informing on the implications of deployment. With fundamental knowledge gaps on background information for modelling parameters, it is currently entirely inadequate to rely on modelling for technologies designed to be released into wild propagating species, as acknowledged by the last AHTEG on RA/RM.It would be appropriate here to mention that a moratorium on gene drive field releases has been demanded by many civil society organisations (ETC Group 2018, Bassey-Orovwuje et al. 2019).Bassey-Orovwuje, M., Thomas, J. & Wakeford, T. Exterminator Genes: The Right to Say No to Ethics Dumping. Development 62, 121–127 (2019). https://doi.org/10.1057/s41301-019-00214-3ETC Group 2018 United Nations Hits the Brakes on Gene Drives. <https://www.etcgroup.org/content/united-nations-hits-brakes-gene-drives> Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. <https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/>  |
|  58 | 34 | We strongly support this acknowledgement that risk assessments based on lab experiments and modelling cannot be relied upon (same references as p.58, line 28). |
| 59 | 3-5 | The statement that unintended changes are not unique to genome editing and expected to be significantly lower than rates of spontaneous mutations or chemical mutagenesis, is omitting accumulating evidence of a wide array of unintended effects including on-target translocations, rearrangements, large-scale deletions and insertions, including insertion of exogenous DNA (and RNA-derived DNA templates) into edited cells, and the high-frequency production of aberrant proteins (e.g. Bruner et.al., (2019; Kosicki et al., (2018); Tulhadar et al.,(2019)).Moreover, evidence is accumulating that contradicts the assumption that nuclease-induced DNA breaks are repaired equivalently to naturally arising mutations, with evidence of increased levels of erroneous repair (Brinkman et al., 2018), and deployment of error-prone alternative DNA pathways not prescribed as resulting in SDN-1, 2 or 3 outcomes as widely assumed including alternative end joining and or combined with RNA-mediated DNA repair (Liu et al., 2021; van Overbeek et al; Ono et al., 2015). Unintended genomic changes are not routinely assessed, and are often missed unless more thorough analyses are performed. *This sentence should thus be removed, or altered to reflect the accumulating evidence that goes against the assertion that imprecision of genome editing is lower than natural mutations or classical mutagenesis, and instead reflects potential risks to biodiversity, and human health as a result of unintended changes at the level of the genome.*Brinkman, E. K., Chen, T., de Haas, M., Holland, H. A., Akhtar, W., & van Steensel, B. (2018). Kinetics and Fidelity of the Repair of Cas9-Induced Double-Strand DNA Breaks. *Molecular Cell*, *70*(5), 801-813.e6. <https://doi.org/10.1016/j.molcel.2018.04.016>Bruner E, Yagi R, Debrunner M, Beck-Schneider D, Burger A, Escher E, Mosimann C, Hausmann G and Basler K (2019). CRISPR-induced double-strand breaks trigger recombination between homologous chromosome arms. Life Sci Alliance 2(3), pii: e201800267Kosicki M, Tomberg K and Bradley A (2018). Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. Nat Biotechnol 36, 765-771Leibowitz ML, Papathanasiou S, Doerfler PA, Blaine LJ, Sun L, Yao Y, Zhang CZ, Weiss MJ, Pellman D (2021). Chromothripsis as an on-target consequence of CRISPR-Cas9 genome editing. *Nature Genetics*. 53(6):895-905. doi: 10.1038/s41588-021-00838-7. Liu, M., Zhang, W., Xin, C., Yin, J., Shang, Y., Ai, C., Li, J., Meng, F., & Hu, J. (2021). *Global detection of DNA repair outcomes induced by CRISPR-Cas9* [Preprint]. Genomics. <https://doi.org/10.1101/2021.02.15.431335>Ono, R., Ishii, M., Fujihara, Y., Kitazawa, M., Usami, T., Kaneko-Ishino, T., Kanno, J., Ikawa, M., & Ishino, F. (2015). Double strand break repair by capture of retrotransposon sequences and reverse-transcribed spliced mRNA sequences in mouse zygotes. *Scientific Reports*, *5*, 12281. <https://doi.org/10.1038/srep12281>Tuladhar R, Yeu Y, Tyler Piazza J, Tan Z, Clemenceau JR, Wu X, Barrett Q, Herbert J, Mathews DH, Kim J, Hwang TH and Lum L (2019). CRISPR-Cas9-based mutagenesis frequently provokes on-target mRNA misregulation. Nat Commun 10, 4056, doi: 10.1038/ s41467-019-12028-5van Overbeek, M., Capurso, D., Carter, M. M., Thompson, M. S., Frias, E., Russ, C., Reece-Hoyes, J. S., Nye, C., Gradia, S., Vidal, B., Zheng, J., Hoffman, G. R., Fuller, C. K., & May, A. P. (2016). DNA Repair Profiling Reveals Nonrandom Outcomes at Cas9-Mediated Breaks. *Molecular Cell*, *63*(4), 633–646.ENSSER (2021) “Scientific critique of Leopoldina and EASAC statements on genome edited plants in the EU”: <https://ensser.org/wp-content/uploads/2021/04/Greens-EFA-GMO-Study-1.pdf>  |
| 59 | 15 | We strongly reject the suggestion that a “Risk assessment light” could be used for the regulation of genome editing due to many uncertainties in the edited crop constructions, as well as the high likelihood that, like in the case of GMOs, it could cause harm to the environment, crop relatives and the health of peasant farmers and ultimately consumers. |
| 60 | 32 | We agree that additional research is necessary to assess the risk of these technologies before they are considered to be released into the environment. |
| 61 | 24 | This should include the fact that epigenetic changes can be inherited, which is an additional risk to ecosystems and biodiversity. |
| 61 | 32 | There are no current examples of “build-in safety features”, only speculation. Also applies to “kill switches” (p.62 Line 11). |
| 68 | 6 | dsRNAs are explicitly designed to modify genetic activity of exposed organisms, with some effects potentially hereditary, and thus can be considered a genetic modification technique. Industry patents have been filed that claim heritability, as well as proprietary rights over exposed organisms and their offspring. Any proposals to regulate solely the dsRNA product and not the exposed organisms thus fails to acknowledge the biosafety and socioeconomic implications of this new form of genetic modification. The document states that products based on RNA-based technologies could be considered “non-transgenic” (and thus could avoid total or partial biosafety evaluation), when the paper has already acknowledged risks of epigenetic change from the RNA that has been introduced (see note on p.61 Line 24). This needs correcting as, otherwise, the Singh et al. (2019) paper cited risks misleading the reader. |
| 71 | 24 | We suggest the addition of this sentence at the end of the paragraph: “In fact, given that gene drive applications have the potential to cause serious harm to the environment, which is a public good, it would not be appropriate to place regulation and decision-making about the technology solely in the hands of private actors.” Lim, L.C., & Lim, L. L. (2019). *Gene Drives: Legal and Regulatory Issues*. Third World Network. <https://www.twn.my/title2/books/Gene-drives.htm> |
|  130 | 24 | Indigenous Peoples and Local Communities IPLC) will require resources to conduct their own collective discussions and decision making as part of adequate FPIC (wrongly abbreviated to FFIC on line 23). Their should be an obligation to provide these resources. |
| 134 | 20 | Insert the sentence: “FPIC should follow principles that are proposed by IPLCs themselves, which will differ depending on their cultural, geographical and political contexts”. |

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