**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** | |
|  |  | **Please note that this document contains collected comments of members of the Max Planck Society and is accompanied by an additional document, in which we comment on several issues with the overall text:**   1. **Lack of clear definition of the term "synthetic biology" and motivation to differentiate from existing regulatory processes** 2. **Need of a clear statement on the regulation of synthetic biological applications (Products or methodology should be evaluated?)** 3. **Lack of commitment to objective, fact-based decision-making for regulatory affairs** 4. **Weighing risks and benefits fairly, including discussion of alternatives during decision-making** 5. **Problems of limitations of scientific freedom and open science through overarching regulations** 6. **Problem of economic considerations impeding basic science** 7. **Intransparent review process and lack of participation of experts** | |
| 8 | 6 ff | A potential risk to biodiversity only arises from the release of organisms to the unmanaged or wild setting. As such, any product (either created through classical breeding, GMO or synthetic biology) should be treated equally, especially since product created through single-base editing are in principle even better controlled. It should also be noted that CRISPR/Cas9 gene editing efforts that result in single-base changes, which are also naturally occurring and/or could be the result of spontaneous mutation are not considered GMO. | |
| 8 | 9 ff | A fundamental difficulty with the text is that it does not precisely define synthetic biology and make a clear case why it should be regulated differently from processes such as GMO, genome editing (CRISPR-cas9) and gene drive that are already widely discussed by regulators. This is already an issue in the Executive summary, where it is vaguely mentioned that synthetic biology (page 8 lines 9-20) “relies on a suite of supporting technologies and tools” but the only specific examples mentioned are CRISPR-cas9 and gene drive. Also, on pages 30-34 most of the examples given are straightforward use of CRISPR-cas9 for single gene knock outs. The authors seem aware of this (page 15, line 21), as the document states “the broadest interpretation has been made in order to be as inclusive as possible whilst at the same time not championing this interpretation as being definitive”. But the breadth of the definition makes the document very difficult to assess or engage with. I suggest that they provide a clear, precise definition of synthetic biology as they interpret it and state exactly how this differs from the specific technologies they mention that are already heavily discussed by regulators. | |
| 8 | 42 ff | It is unclear, why synthetic biology is singled out compared to other human activities affecting biodiversity (e.g. agriculture, plant breeding, land use, etc.), especially given the fact that synthetic biology or more accurately (single-base) genome editing is much more precise and targeted than traditional plant breeding efforts. The product and not the method that was used to create the product should be evaluated. | |
| 8 | 44 ff | “*Calls for improved governance of synthetic biology, including addressing gaps in the international legal and regulatory frameworks, place significant emphasis on the need to better address challenges that go beyond the scientific areas, and call to also consider societal, economic, and ethical dimensions.*” This comment seems poorly defined and delimited. Moreover, these broader issues certainly require an analysis of each potential product individually and not the process of synthetic biology. Vagueness on these societal issues also arises later on page 11 (line 15), where no detailed examples or references are used to raise a number of hypothetical potential problems. “There may be the need to consider creating rules for specimens produced from synthetic or cultured DNA as the demand for them could not only lead to an increase in the demand for (illegal) natural specimens, but they could also be mixed with (illegal) natural specimens. The displacement of some of the natural products (i.e. naturally occurring molecules obtained from plants) can also potentially ease negative pressures on wild or cultivated species, but it can also displace cultivation practices, often in topical and sub-tropical regions.” | |
| 9 |  | The use of gene drives is a very extreme example for genetic engineering and not exemplary for “synthetic biology”. There is a tendency to use “gene drives” as an extreme example for a product. Per se the “product” and its consequences, but not the methodology that was used to create the product should be evaluated. | |
| 10  16 | 1 ff  26 ff | Most of the examples (or products) are rather considered classical GMOs and not “synthetic biology” | |
| 14 | Table | Some of the genome-edited plants listed would not be considered “synthetic biology” products, but rather products of classical genetic engineering. Some plants would be eventually even not considered GMOs (in case of single-base modifications that occur also naturally). Again no clear definition of “synthetic biology” | |
| 14 | 34 ff | *Often, international and national regulatory regimes tend to focus on biosafety risks rather than a more holistic approach that takes into account a range of public interest issues related to the biosecurity, ethics, societal, cultural and economic implications of synthetic biology more broadly, as well as potential benefits related to biodiversity conservation and sustainable use. In this sense, a new paradigm for regulating synthetic biology applications is needed that looks beyond just biosafety*”  It should be cautioned against bringing broader policy and societal issues into regulatory issues related to synthetic biology in the CBD. A more pragmatic way forward is an evidence-based approach, including evidence-based decision-making by the scientific community on a case-by-case basis to avoid violating biodiversity and sustainability goals. | |
| 15 | 13 ff | Use of “synthetic biology” as very inaccurate “blanket definition” for classical biotechnological efforts. | |
| 24 | 37 | This example is classical protein engineering, but not synthetic biology | |
| 27 | 1 ff | Unclear, why protocells and/or cell-free systems are classified as synthetic biology, also unclear why these systems are considered in the context of CBD, as they do not replicate and/or evolve. | |
| 33 | 13 ff | “Synthetic” microbial communities do not necessarily involve the use of modified microbes, but typically the defined composition of a microbial community from naturally existing strains. Usually no synthetic biology or genetic engineering involved. | |
| 34 | 8 | Describes transient modifications | |
| 38 | 22 ff | Protocells and/or viruses are not organisms | |
| 48 | 19 ff | Potential negative impacts are attributed to the technology that are not technology-specific, but rather broader social practices for example over-farming/aggressive monopoly business models. | |
| 50 | 16 ff | “*However, the degree to which a risk is acceptable cannot be determined purely scientifically; science can predict the likelihood of certain effects, but non-scientific criteria must be included in the process of judging their acceptability*”.  A big concern in this statement is the lack of a clear commitment to scientific theory and fact-based argumentation as guiding principle for decision-making. We agree that there is a need for scientific bodies to continuously engage in dialogue with the public and to increase the quality of that dialogue, as well as a need to promote transparent information sharing. However, there also needs to be an in-principle agreement on the possibility of attaining an objective definition of risk. We would strongly caution against bringing broader policy and societal issues into regulatory issues related to synthetic biology and instead strongly favour an evidence-based approach, including evidence-based decision-making guided by the scientific community on a case-by-case basis to avoid violating biodiversity and sustainability goals.  While it is important to consider societal and ethical concerns relating to synthetic biology research and applications, we find it also important that potential and realized benefits to society and environment are widely publicized for an informed discussion in the public. Considering the polarized and emotionalized discussion on the generation and release of genetically modified organisms in the past, we deem it essential to fairly weigh risks and benefits based on a scientifically informed discussion to prevent the ban of technologies that hold significant promise to solve societal and ecological problems. We also would like to stress that any discussion on technologies needs to incorporate considerations of potential alternatives and their benefits and risks (e.g., the use of pesticides versus specifically designed biocontrol agents). We would also like to highlight that many of the risks discussed in the text in general are not related to the specific technology of “synthetic biology”, but rather to broader social practices, such as aggressive monopoly business models. | |
| 58 | 47 ff | The claim that genome editing allows for modifications that would not otherwise naturally arise is in complete ignorance of the entire body of knowledge regarding Darwin’s theory of evolution by means of natural selection. The cited work grossly misrepresents statements made in original research that is cited in support of these absurd claims. For example, Monroe, J. G., Srikant, T., Carbonell-Bejerano, P., Exposito-Alonso, M., Weng M.-L., Rutter, M. T., Fenster, C. B., and Weigel, D. (2020) Mutation bias shapes gene evolution in *Arabidopsis thaliana*. bioRxiv 156752 <https://doi.org/10.1101/2020.06.17.156752>, states that mutations are less likely at some sites in the genome than others but does not claim that mutations at some sites are impossible, as misrepresented by the Kawall et al. reference cited in the report (Kawall, K., Cotter, J., & Then, C. (2020). Broadening the GMO risk assessment in the EU for genome 6 editing technologies in agriculture. Environmental Sciences Europe, 32(1), 106. 7 <https://doi.org/10.1186/s12302-020-00361-2>). | |
| 61 | 7 ff | It is not clear how the discussion on ”off-target” effects in plants with genomes of different sizes informs on specific risks. CrispR is in fact, a cleaner technology than classical mutagenesis (which is already proven safe and societally valuable with currently used crop varieties), and now with whole-genome sequencing, the genetic material considered in each case can be precisely evaluated. Further “Largely missing from this conversation, however, is attention to local communities in decision-making which are likely to be the first to feel any potential impact from these applications (Kofler et al., 2018)”. It is unclear what type of cost that local communities will bear e.g. upon the cultivation of a maize CrispR line. | |
| 67 | 11 ff | The discussion of detection of genome edits reflects a thorough lack of understanding of limitation of such detection methods. For a more balanced and nuanced treatment of the matter, see, for example, Huang, S., Weigel, D., Beachy, R. N., and Li, J. (2016) A proposed regulatory framework for genome-edited crops. Nat. Genet. 48, 109-111 <https://doi.org/10.1038/ng.3484>. | |
| 109 | 85 ff | “potential impacts of very low probability but very high magnitude”. This statement is so broad that it is very difficult to discuss properly. Such considerations make sense to discuss only when evaluating a specific, pre-defined, concrete risk situation. | |
|  |  | Additional rows can be added to this table by selecting “Table” followed by “insert” and “rows below” | |

Please submit your comments to [secretariat@cbd.int](mailto:secretariat@cbd.int).