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| **Comments on the Technical Series on Synthetic Biology** |
| **Page #** | **Line #** | **Comment** |
|  |  | The 2021 draft of the Technical Series on Synthetic Biology is a welcome update to the original edition issued six years earlier. The draft covers an impressive number and breadth of publications on the topic. I have a few general suggestions for improvement before a final version is issued. First, the more detailed sections, i.e., Sections C, D, and E illustrate well the wide range of potential applications of synthetic biology, the breadth of the technologies, and hence the significant governance mechanisms that currently exist. However, the Executive Summary (Section A) and Conclusions (Section F) all too often state generalizations that are just too broad to be accurate for many, and in some cases, most situations. I appreciate the need for brevity in these sections, but this should not be at the expense of accuracy. Given that most readers will only read these summary sections, fewer generalizations and greater specificity will give readers a better understanding of the issues.Second, Section E (Governance) covers international governance in far greater detail than national and self-governance (50 pages vs 6 pages). Unfortunately, this does not give the reader a firm foundation from which to judge gaps and overlaps in overall governance and thus what is needed from international governance. A discussion of how these governance arrangements fit together would be very helpful.Third, the document covers the risk from applications of synthetic biology in greater depth than the benefits. Though only indicative, a quick search reveals the term risk appears 398 times in the document; the term benefit appears 206 times. Risks of synthetic biology applications are often presented without an explanation of the risks and harms the problems they hope to solve or from the technologies they hope to replace. Providing additional context from risk-risk and risk-benefit perspectives would be helpful when specific applications are discussed. |
| 9 | 3-11 | The unwarranted generalization of this closing paragraph of the executive summary contradicts the far more balanced previous page, which recognizes that applications of synthetic biology are many and varied and “cannot be generalized” (page 8, line 29). Nations focus their governance of most products on biosafety, human health, and the environment for good reasons. A few products may require a “more holistic approach” as described in the paragraph, but to generalize this to all applications that use the tools of synthetic biology is not at all justified by most of the examples discussed throughout the report or the quite comprehensive review of the technical literature. |
| 9 | 34, 35 | Hyperbole may make for more interesting reading but is less accurate. Synthetic biology’s potential is not boundless, nor will its’ impacts be unprecedented.  |
| 9 | 49 | After an informative list of applications, the statement that these applications could have an impact in an unprecedented manner is not justified and is not accurate.  |
| 10 | 19, 20 | Plant synthetic biology is lagging behind bacteria and yeast, but not behind mammalian systems. As described later in the text, there is considerable activity, both in product development and development of new tools, for use in agricultural plants.  |
| 10 | 37-39 | While the text of the paragraph below is informative, the title is neither accurate or a summary of the paragraph itself. The public at large will have greatest interactions with products from contained settings. Those that have attracted greatest attention are those intended for wild settings, even though they are in the earliest stages of development. The title should just describe that organisms modified using the tools of synthetic biology are varied, with most intended for use in contained settings, followed by those intended for managed settings, and a few for wild settings. |
| 11 | 6-8 | I think the sentence on p.9, lines 29-31 is more accurate. Rather than being informed by actual experience with LMOs, the current debate just echoes concerns expressed at the emergence of classical genetic engineering.  |
| 11 | 30-34 | This paragraph again strays into the territory of sweeping generalizations. While IPLCs will be affected by some products of synthetic biology, for most products there is no reason to believe that they are “most likely to be impacted first” (line 31), thus no compelling reason why early engagement with IPLCs should be singled out. If this paragraph is about natural products such as vanillin (as discussed in the preceding point 8) or gene drives, be specific. |
| 11, 12 | 42-51, 1-7 | Again, a sweeping generalization. The paragraph implies, and line 49 states, that any product made with synthetic biology somehow requires greater public engagement in regulatory decision-making. Please identify the type of products for which you are recommending this type of enhanced engagement. |
| 12 | 23 | First part of sentence missing. |
| 12 | 37, 38 | Again, I see no justification for the recommendation that a new paradigm is needed for regulating products of synthetic biology. This may be the authors’ policy preference, but it is not a conclusion that has been justified in the document. If the authors are referring to particular types of products, please be specific. |
| 13 | 5-7 | The statement in point 14: ‘Adapting existing frameworks in order to “future proof” them for synthetic biology’, in my view, is a more justifiable and accurate statement than that a “new paradigm” is needed, as stated in point 12. |
| 16 | 33,34 | Perhaps “coordinated” international regulatory environment is a better term than “cohesive” regulatory environment. This would be a good place to at least name the other international players discussed in the full document, e.g., WHO, FAO, WIPO, etc. |
| 18 | 2,3 | Clarify that benchtop DNA “assemblers” have been available for several years (Codex DNA) but enzymatic “printers” are expected in the next year or two. |
| 30 | 2-26 | The bioremediation, biodegradation, and biomining examples would be better placed in the semi-managed/managed section that follows, rather than wild settings |
| 30 | 12 | Rather than the term “xenobiotic cleanup”, Rylott and Bruce refer to clean-up of environmental pollutants or clean-up of “inorganic and organic pollutants”. |
| 30 | 35 | The gene-drive developed for mice was to help develop medical mouse models and would not work for a biocontrol application. |
| 31 | 27-32 | Unless there is a very recent change, Oxitec insects are still in advanced development stage (as listed on page 32) or research. I am not aware that Oxitec mosquitos can be commercially purchased and other insects are in earlier stages of development. |
| 32 | 20 | Inaccurate heading for this section. “genetically engineered insects for biocontrol” or “self-limiting insects” as on the previous page. |
| 33 | 17,18 | Again, inaccurate heading. None of the papers cited have anything to do with insect delivery. These are examples of virus vectors for genome editing used in the lab. The notion of HEGAAs is an attention-getting headline but implying that the examples listed are “environmental agents” is quite misleading. It is also a bit odd to me that 50% more text is devoted to viral agents for genome editing than CRISPR edited plants and animals on p.31 and 32. |
| 33 | 33 | Incomplete heading. Section includes both “de-extinction” and applications to species close to extinction (though these are cloning). In addition to Przewalski’s foal, you might also include the recent example of cloning to increase the genetic diversity of black-footed ferrets. |
| 34 | 8 | Incomplete heading. I believe several of the examples are RNA pesticides that act directly on agricultural pests. |
| 34 | 34 | Several of the examples in the following 2.5 pages are more accurately described as advanced development. I will point out a few, but I think the authors should reconsider their definition of “commercially available” to include some notion of commercially viability rather than just proof of concept. |
| 34, 35 | 43 | Cellbricks are cell scaffolds, not synthetic biology |
| 35 | 16-31 | I believe most (if not all) of these applications should be moved to “advanced development” |
| 36 | 31-36 | Advanced development more appropriate? |
| 37 | 12-19 | Advanced development more appropriate? |
| 38 | 36-41 | The heading should refer to the application: “Modified horsepox virus to use as a smallpox vaccine.” The company is also researching use of the virus for a COVID-19 vaccine. It is fine to mention that it was re-created in the text, but not as the title. I do not understand the last sentence. There was no physical sample to work with. |
| 40 | 30-34 | Perhaps this paragraph should have been included in the beginning of the Applications section, along with an explanation of the criteria used to distinguish “commercially available” from advanced development. |
| 44 | 35-40 | The most comprehensive review of conventional GMO crops is “Genetically Engineered Crops: Experiences and Prospects”, NASEM, 2016. At minimum, it needs to be included as a reference. A paragraph or two on its conclusions would be a very useful addition. |
| 54 | 33-37 | As a co-author of Garfinkel et al. 2007, I was very surprised to see this extremely speculative statement ascribed to our study. We did not suggest this. The Mukunda paper includes this particular speculation among a long list of possible speculations for the future, one or some of which might happen in more than 10 years. I suggest that these lines be deleted. |
| 5455 | 48-501-14 | This is the second time the “insect allies” research program has been discussed in the report. Why is this much text devoted to what the report describes as speculations? |
| 57 | 14-16 | Such a sweeping generalization is far too broad to apply to all “synthetic biology applications” and as stated, highly misleading about challenges to regulation. In fact, the Duensing article cited as the source of the statement comes to the opposite conclusion in the abstract: “Since genome editing can lead to the development of plants that could also have come into existence naturally or by conventional breeding techniques, there are strong arguments that these cases should not be classified as genetically modified organisms (GMOs) and be regulated no differently from conventionally bred crops.” The introductory paragraph to section 7 (Governance and Regulation) is a much more accurate statement  |
| 6263 | 21-461-49 | Subsections 6.2.3 and 6.2.4 discuss two topics related to gene drives: 1) designs for temporal and geographic containment and 2) post-release removal. The concepts are mixed into both sections in a confusing manner. Headings should clearly refer to gene drives, not generalize to “synthetic biology organisms.” |
| 64 | 20 | Given the extensive discussion of gene drive organisms, one might explicitly point out that such organisms are easily detected with PCR-based methods |
| 65 | 19-32 | This section needs an introduction to Section E, Synthetic Biology Governance. The section includes approximately 3 pages on national regulation, 3 pages on self governance, 20 pages on the CBD, and 30 pages on other international aspects of synthetic biology governance. As correctly stated on p.68, lines 29-30, the majority of regulatory decision-masking will be at the national level. Thus, the section needs an introduction that puts the three forms of governance into perspective. Otherwise, it is impossible to understand and contextualize the governance gaps and overlaps identified in the 50 pages devoted to international governance. Expanded discussions of national regulation and self governance would also be useful, if time permits. |
| 65 | 42-44 | This statement is misleading. The sentence, and the 2.5 pages that follow, make it appear that the only applications of synthetic biology that have received regulatory review and attention are those that employ genome editing, gene drives, and RNAi technologies. This is by no means true. Most products of synthetic biology are well-covered by current regulatory regimes for biotechnology, as briefly covered in section 7.2. The three technologies highlighted in 7.1 are examples of those that have received additional scrutiny.  |
| 65-69 |  | Following the comment above, I think reversing the order of sections 7.1 and 7.2 will give readers a more accurate understanding of national regulatory frameworks for synthetic biology. |
| 7071 | 33-471-12 | This section mixes calls for moratoria with discussions of self-regulation. Line 41 (p.70) is clearly contradicted by Lines 13-24 (p.71) and subsections 7.3.3 and subsections 7.3.4. I suggested deleting lines 41-47 (p.70) completely.  |
| 71 | 13-24 | This paragraph discussing establishment of community norms is incorrectly included in the subsection on calls for moratoria. This deserves a separate subsection. |
| 76 | 8-11 | This is incorrect and misleading. Most of these areas of research cannot be categorized as “living” vs “non-living”. For example, one can engineer a non-living genome, but the reason for doing this is to use it in a living organism. This applies to most of this list. Cell-free systems, however, are non-living.  |
| 90 | 1-5 | The notion that vaccines and biologics are not “addressed by other international agreements or organizations” strikes me as very odd. World Health Organization, International Council for Harmonization, and many other international bodies address pharmaceuticals, including vaccines and biologics. |
| 126 | 11-15 | I think it is important to point out that this is as it should be. Synthetic biology is too broad a collection of tools and can be applied to so many and varied applications that “no specific governance… on an international scale” would be possible or appropriate. |
| 127 | 20, 21 | This is not correct. Nefarious applications of synthetic biology have been discussed under the Biological Weapons Convention. |
| 128 | 26 | Following section “10.1 Risk of Harm,” the report needs a section “10.2 Balancing Risks and Potential Benefits.” In my opinion, this is the single greatest challenge associated with synthetic biology governance (the topic of Section 10). Though the report stresses the varied nature of the products using synthetic biology techniques, Section 10 overlooks this. How one balances risks and harms from simple crop genome editing (e.g., SDN-1) vs gene drives will be very different. Some of this is alluded to in lines 15 through 19 on this page. The WHO will view gene drives “through the lens” of 500,000 deaths/year from Malaria. FAO will view genome editing through the opportunities it provides for food security. |
| 128 | 48 | Subsection 10.3 omits the potential benefits from the tools of synthetic biology as enabling technologies that will allow countries to benefit from their own genetic resources. “Classical” 20th century tools of biotechnology were far less capable for harnessing genetic resources in productive ways. This is not just as issue of DSI. |
| 129 | 25, 26 | Again, “synthetic biology” covers too many technologies to allow such general statements as “many potential synthetic biology organisms may not be easily detectable”. This is true only when the changes to the genome are so minor as to not be differentiated from mutations that might occur naturally. |
| 129 | 32-33 | This is a very odd way to characterize an article that concludes “synthetic biology is at the cusp of many major breakthroughs.” Glass half empty vs glass half full… |
| 129 | 34-37 | Of course there is a “knowledge gap” in how nature works. The authors should explain that the T and L in DBTL stand for “test and learn” and the reason it is called a “cycle” is that process is iterative, with redesign based on the knowledge gained through each iteration. This is one of the most powerful aspects of synthetic biology. Narrowing the knowledge gap about how the organism works is very much part of the process. |
| 130 | 6-8 | I do wish that the authors would expand on the lessons learned from “previous experience with classical genetical engineering”. Again, the most authoritative review I know of is “Genetically Engineered Crops: Experiences and Prospects”, NASEM, 2016. This would be helpful for readers who have only heard the “hypothetical/speculative concerns. |
| 130 | 14-38 | Again, such broad generalizations about synthetic biology are not warranted nor are they helpful. Do all applications of synthetic biology require “inclusive decision-making and community engagement”? I hope the authors do not mean to imply that most synthetic biology research is irresponsible, but that is the conclusion from such sweeping and misleading generalizations. Is FPIC appropriate for all applications? This section needs to be sharpened, with generalizations deleted. |
| 131 | 36-38 | Another sweeping generalization that is misleading. As pointed out earlier in the document, most products will be adequately covered by existing governance frameworks. Others are being adapted in real time (e.g., genome editing), as pointed out in several reviews referenced in the report. Clearly some are posing challenges. |
| 132 | 7-30 | I agree that gene drives “provide a useful lens” for considering the governance of at least a few of the proposed applications of synthetic biology. (I also agree with the conclusion stated in lines 27-30.) But when presented as the sole “lens”, it is actually quite misleading. Another example (perhaps genome editing, products intended for contained use, or even both) would illustrate the difficulty and even danger from attempting to draw general conclusions about such a varied set of potential applications as is anticipated from synthetic biology.  |
| 133 | 21-23 | Rather than referring to the discussions in Section 5, I think it makes more sense to review the applications discussed in Section 3. Yes, some will “challenge regulatory oversight”, most will not.  |

Please submit your comments to secretariat@cbd.int.