**template for Peer Review comments**

**Technical series on synthetic biology**

|  |  |  |  |
| --- | --- | --- | --- |
| **Contact information** | | | |
| **Surname:** | | | Steinbrecher |
|  | | |  |
| **Given Name:** | | | Ricarda A. |
|  | | |  |
| **Government** | | |  |
| **(if applicable):** | | |  |
|  | | |  |
| **Organization:** | | | Federation of German Scientists & ENSSER |
|  | | |  |
| **E-mail:** | | | r.steinbrecher@econexus.info |
|  | | |  |
| **Comments on the Technical Series on Synthetic Biology** | | | |
| **Page #** | **Line #** | **Comment** | |
| 0 | General comment | The report lacks balance, it shows a strong bias towards assumed benefits without acknowledging its own assumptions and without providing the required scientific basis and analysis.  Throughout it exaggerates benefits and possibilities of synthetic biology and its applications.  It unfortunately comes across as suffering from an inability to distinguish between exaggerated claims and actual possibilities. | |
|  |  | There is often little actual information to back up assertions and when making them, the report would benefit from clarifying whose opinions these are and keeping its own distance, ie not presenting these interpretations as its own, but offering different sides and interpretations in an honest manner. | |
| 0 | General comment | Fails to provide the full picture, range and intricacy of the issues, concerns and risks | |
|  |  | It lacks contextualisation in terms of differentiating between symptoms (as a result of underlying problems) and the problems themselves and their underlying causes - and the search for sustainable, long-term solutions, which will require change of practices and the ecosystem approach.  It seems to favour technical ‘solutions’ over the (eco)systems approach and fails to give space to or even acknowledge other paths and practices towards real solutions, e.g. in agriculture and climate adaptation. Here traditional knowledge, especially that of Indigenous Peoples and local communities and smallholder farmers has a critical role to play. | |
|  |  |  | |
|  |  |  | |
|  |  | The term “application(s)” would benefit from a clear definition either throughout or whenever it is used, as its use and meaning is not uniform throughout the report. It may mean each time a technology is used, it may mean a general area of use, etc ... Please check and adjust. | |
| 8 | 6-7 | The phrasing “the potential of synthetic biology carries hopes and aspirations to address a multitude of global challenges related to ....” is merely an opinion about the potential of synbio that is not agreed by all, nor is it viewed as the instrument of choice to address the global challenges and multiple crises. The overemphasis on benefits and the effort to portray synthetic biology applications as solutions means the reader cannot easily see the broad picture and the context in which the debate and the crises are happening.  The importance of a systems approach and the ecosystem approach to many of the challenges is not given any space. Yet we would require exactly that bigger picture and the analysis within the systems approach to understand and assess the examples presented in this report. | |
| 8 | 8 | “about ~~potential~~ risks...”: delete “potential” as risks are defined as the likelihood of a harm to occur, i.e. it already entails the “potential” | |
| 8 | 10 | ~~Sophisticated~~ perhaps say ‘advanced’ - | |
| 8 | 11 | “applications” - please clarify what is meant and that this refers to research settings, not applications in the ‘real world’ so to speak. | |
| 8 | 12 | “has increased exponentially” - who says so? It is also not referenced later. Are you referring to number of publications? And over which time period? | |
| 8 | 13-15 | “ .. is having impacts in agriculture, especially in increasing plant yield, quality, disease resistance and herbicide resistance, breeding, and accelerated domestication.”  CRISPR/Cas technology has not yet had any impact on agriculture. There are no CRISPR-modified crops in the fields. There is no data on real life performance trials (including under different environmental conditions, in the presence of different biotic and abiotic stressors, and across a longer time span) of genome edited modified crops that shows yield increases (what please is meant by “plant” increase?) that would allow for such a statement. This statement needs removing or urgent adjustment - as it does not depict the reality.  Furthermore, ‘accelerated’ domestication comes with its own risks and it will require much further work and investigation to assure safety and reliable agronomic performance with such an approach. | |
| 8 | 23 | This is not just to “support the discussions” but to support the assessment and the ongoing deliberations | |
| 8 | 26 | ‘science based assessment’ - this concept requires a broad interpretation, not a narrow one, in order to ensure the inclusion of different knowledge systems and a broad multi- and inter-disciplinary process. | |
| 8 | 28-30 | Please adjust to clarify and present that there are categories and groupings with common factors that would benefit from an overall assessment, in order to understand which questions need to be asked, how to identify potential harms and which potential harms should be considered and how to assess them. This is also behind the need to provide guidance materials for risk assessment and risk management for specific categories of LMOs. It should only be after such wider assessments and considerations, and in that context, that individual applications can move forward on a case-by-case basis. | |
| 8 | 32 | “classical genetic engineering” - this term is misleading and rarely used. It could be “first generation” or simply “previous” - although it is still a current form of genetic engineering. | |
| 8 | 33 | Please replace ‘albeit’ with “, possibly” - as it will depend on future deliberations and the decisions made by individual parties. | |
| 8 | 37 | The word matter is ambiguous – replace with issues | |
| 9 | 14 onwards |  | |
| 9 | General comment | The headings of the Key Messages under the section of “current state of synthetic biology” - in particular messages 1, 2, 3 and 4 would benefit from adjusting, as they contain misleading claims, exaggerations and language that does not befit this report. The way it is presented portrays an over-enthusiasm for the technologies and a clear bias. It would be best to write new headings that are more fitting and neutral and factual in their presentation. | |
| 9 | 17 | The heading reads:  “Synthetic biology is a cross-cutting and rapidly advancing discipline that has gained great attention due to its increasing relevance to the environment, food and health among other global challenges.”  Firstly, this heading is the wrong kind of heading for the text that follows, as the text looks at what is considered synbio, its regulation, views about synbio and the challenges to consensus building.  Secondly, this heading is a making a claim that is unsupportable, biased and misleading. Synbio has gained great attention **not** because of a supposed increasing relevance (in particular to the environment, food health and other global challenges), but because of its claims and promises, and the power of these claims and promises to capture the headlines and possibly minds. Sociologists argue, that underlying this is the desire to believe that technology can help us to continue with business-as-usual but avoid disaster. | |
| 9 | 28 & 29 | ‘classical’ - see comment page 8, line 32 | |
| 9 | 28 | ‘albeit’ - see comment page 8, line 33 | |
| 9 | 32 | After ‘biodiversity related issues’ ADD “,including human health” | |
| 9 | 34 | Key Message 2: “The potential of the synthetic biology toolbox is boundless, and so are the opportunities for synthetic biology to have an impact in an unprecedented manner.”  As before, this is more befitting to a synbio press release or PR document than a technical CBD series. How is the potential of a toolbox boundless? And why or how are the opportunities to impact boundless, and what is implied by an “unprecedented manner” ? It is a heading full of superlatives offering little help for the tasks at hand, in particular when the reader is expecting to be given some actual information on the current state of synthetic biology.  If you intend to keep the heading, please ADD “and risks” after ‘opportunities’ to give at least a hint of balance. | |
| 9 | 36 | When referring to the “numerous” applications that have reached the market please specify what they mostly are (e.g. flavours and fragrances, contained use applications, ...) to help focus the mind rather than being drawn to speculation. | |
| 9 | 37-39 | Please ADD “under development” after “Some of these applications”.  Please check (and clarify) if you mean that the applications suggested here are to address climate change itself or the impacts of climate change, i.e. here the effect of the warming of the ocean.  When referring to climate change adaptation, the Corals example given is one where research is in its infancy and it should not be portrayed as if synbio can provide an answer. Please provide an example that does not rely on speculation. You may want to acknowledge however, that climate adaptation and resilience are mostly traits and capacities that grow out of interactions between systems and networks, and adjusting traits within one organism/species is highly complex. | |
| 9 | 40-43 | This sentence does not reflect the crucial nuances presented under section 4.4 which shows that there may also be serious drawbacks and previously unexpected (unpredictable) negative consequences with replacements of natural materials, such as rhino horn. (see also comments for page 47, line 28).  Concerning squalene, whilst this substance was originally sourced from particular sharks, it has long since been obtained from plants, such as olives, and highlighting it here in this context is somewhat misleading. | |
| 10 | 1 | Key Message 3: “The value of the synthetic biology market has increased exponentially”  A few comments:  a) It is not clear why this message is given under “current state of synthetic biology”.  b) I could not find any backup in this report for the claim that the synbio market has increased exponentially. For which period? Is it still doing so? Section 1, page 16, lines 17-21 merely state that the market “has experienced significant growth in the past decade”. Please provide reliable data and sources to back up your statement of exponential growth between 2015 and 2021 or for whichever past period it is correct.  c) If this is a key message it would be important to have a reciprocal extended section in the report, breaking down which aspects of the synbio market/industry are adding to which extent to the growth of the market, providing which products or services. Without such a section the key message appears to have little value and appears more promotional than evidence-based especially since the biggest claim is made about the future, ie: 2021-25. | |
| 10 | 6 | “products”: whist on one hand being products, they are actually largely ‘compounds’ required for research, testing and services (examples given here are synthetic DNA, RNA, oligonucleotides). It would be helpful to differentiate between ‘products’ intended for the release on the market, and ‘products’ that are compounds for use within research and test providers (e.g. for diseases, presence of particular genes, detection of contamination etc). | |
| 10 | 9 | Why are technologies and techniques and capacities constantly portrayed as a “toolbox”? as here a CRISPR-toolbox? It gives the wrong tone and impression when dealing in fact with life-sciences and processes, many of them not fully known or predictable. They are therefore distinct from machines and mechanical processes. | |
| 10 | 10 | Key Message 4: “Supporting technologies and tools have rapidly evolved, spawning even more types and numbers of applications, to the extent that synthetic biology is essentially ubiquitous in life science.”  Firstly, the choice of language is, as with other headings or key messages, problematic and evocative rather than factual, clear and helpful. In particular the term “spawning” “even more” is inappropriate, as it suggests technologies and tools being seen and taken as life and life giver itself. The sense that synthetic biology is now present in all of life sciences is very misleading, as much of it would be due to classic components of genetics research, such as sequencing. The use of nucleotide sequences to test for the presence of genes in populations via PCR is also not synthetic biology, but simply a methodology of modern genetics. By calling almost every approach used a technology of synthetic biology, then the term has lost use and meaning.  Hence please differentiate and resist the further erosion of terms and concepts, thus making discussions and dialogues even harder.  Secondly, and linked to this: it is not clear why there are only “supporting” technologies and tools, as it leaves unanswered the question: what are the actual technologies that are being used? When relating to section 1 (starting page 16) it would be important to differentiate between essential techniques or processes of synthetic biology and supporting technologies and processes, with the latter not being viewed as synthetic biology as such. | |
| 10 | 23 |  | |
| 10 | General comment | Please see comments section 1 page 17, as that section is the basis for the text of the summary, and amend this section of the summary accordingly | |
| 10 | 25 | It should be “by 2016” or “by end of 2015”, as Shapira et al. 2017 did their search between 2000-2015. Preferably it should say something like: “Between 2000 and 2015 some 8064 publications were identified linked to synthetic biology, including patent documents, indicating that more than .......... | |
| 10 | 26 | It is incorrect to say “since 1980”, as the term and concept of synthetic biology were not around then. Equating it simply with Genetic Engineering would not be helpful. Please check and clarify. | |
| 10 | 29 | “the authors reported” - it is not clear who is being referred to here. | |
|  |  |  | |
| 10 | 37 | Key Message 6: “Synthetic biology products designed for use in managed, semi-managed and urban situations attract the greatest attention as those are the ones that the public at large will have greatest interactions with.”  This is the beginning of the new subsection ‘*Potential impacts from synthetic biology*’.  It is not clear at all how this heading is related to potential impacts. It is also not clear whose attention is being attracted here? Policy makers? Press? Funders? Risk assessors?    It might be more helpful to say that LMOs produced through synthetic biology are about to move out of the lab into the field (if that is what the authors of this draft have found and want to say here).  Yet neither of such headings however reflect what is covered in the text that follows. | |
|  | General comment | The text does not give any details relevant to the section title *‘Potential impacts from synthetic biology*’. It merely lists the state of play and of development, which would be more suitable for the previous section.  Another problem is that the piece does not seem to recognise - or fails to portray - the difference between a laboratory setting and an ecosystem: in the former there is more possibility for control than in the latter. There is much we do not understand about the interactions within ecosystems and we have to accept this, not imagine we can overcome it with the correct tools or tailoring. | |
| 10 | 40 | “Synthetic biology has provided an unprecedented toolbox for tailoring organisms for new applications and products.”  If this section is meant to cover impacts, and it starts with “tailoring” organisms for new applications, a clear impact seems to be that organisms are no longer perceived as part of ecosystems and having a standing on their own, but rather as something that one tools and tailors according to perceived wishes and requirements.  This is deeply concerning, as it depicts the lack of recognition and thorough understanding of the complexity of living systems, including ecosystems, and their interactions and interdependence.  However, given this is going to be a document under the CBD, and the CBD has a long history of understanding ecosystems and of working towards the conservation and sustainable use of biodiversity, this introductory sentence should be rephrased, to place synthetic biology within the context that the CBD has debated for the last 8 years.  As often reiterated at CBD meetings and also recognised at IPBES there are different kinds of knowledge systems, including western science; the knowledge held by Indigenous Peoples and local communities and peasant farmers is deeply interconnected with their local ecosystems and must be respected. This is one of the particular aspects of the CBD, that it seeks to do so. As discussed and acknowledged by the AHTEG on synthetic biology, this knowledge is of a very different nature to that connected with synthetic biology. | |
| 10 | 45 | If this refers to the Oxitec RIDL mosquitoes or insects, we consider these to be still at the testing stage (see comments later) | |
| 10 | 46-47 | We consider engineered gene drives to also belong to the category of unmanaged and wild settings and not to be limited or limitable to managed or urban settings. | |
|  | 51 | this sentence does not make sense. Also there seems to be too much emphasis on interactions between people and these applications | |
| 11 | 1 | I suggest to ADD “or release” after ‘for direct use’ | |
| 11 | 4 | This should clarify that it is the impacts of ‘synthetic biology applications (LMOs and products) released into the environment’ on the conservation and sustainable use ....  This is important, as the impacts on conservation and sustainable use from synbio products that are marketed to replace natural products is possible to monitor and assess already. In fact it should have started as a matter of urgent inquiry once marketing started to assess the consequences on livelihoods and conservation and sustainable use of biodiversity. Moreover, there is no mention of the application of the precautionary principle here, which is fundamental to the CBD and could point towards conclusions that can already be drawn BEFORE any release has taken place. Please attempt to adjust. | |
| 11 | 6-10 | More time and experience will be needed before decisions on this point can be made. There should not be a rush but rather a time for investigation and detailed observation to gather sufficient data for future decision-making on this matter. | |
| 11 | 14-15 | ALTERATION:  Please consider the following bold additions to the first sentence:  For example, the replacement of natural products with products resulting from synthetic biology could **in some cases possibly** lessen the pressure on natural habitats **and specific species** but could also disrupt **or undermine** *in situ* conservation projects. | |
| 11 | 16 | Please define ‘specimen’ in this context | |
| 11 | 19 | ADD : ....molecules **and compounds** .... | |
| 11 | 20 | ADD: ... practices **and livelihoods** | |
| 11 | 21 | DELETE: , this ~~therefore~~ may bring | |
| 11 | 29 | Key message 9 | |
|  | General comment | This section lacks a reflection on deliberative process, which is a helpful and promising approach when trying to understand problems and find solutions.  This section would also benefit from adding the much discussed public concern of “need”, and the assessment of need, so that the issue is not solely limited to safety measures and policy but also to defining needs and solutions. | |
|  | 51 | ADD: of environmental and security concerns **and needs**, | |
| 12 | 4 | ADD: ..importance of participatory **and deliberative** decision making | |
| 12 | 10 | COMMENT: it should not only be with regards to intentional misuse but also unintended. | |
| 12 | 11 | ADD: ... public health, **environmental integrity, food production, livelihoods** and/or | |
| 12 | 20 | Self-regulation should not be an option. We need obligatory rules, as it is a matter of public safety and possibly national importance. Biosecurity issue and dual –use are far too important to be left to the researcher to highlight; furthermore the problems may not be immediately evident but emerging gradually. | |
| 12 | 23 | DELETE rogue ;) sentence: there is a problem here – only part of a sentence appears. | |
| 12 | 27  &  General comment | Key Message 12: “For synthetic biology to live up to its perceived (by whom?) potential, an enabling (for whom?) policy and regulatory environment is needed.” This portrays an assumption that synthetic biology is desirable and should be facilitated as much as possible, without saying why or adding other views in balance.  This is not a CBD issue. The precautionary principle offers sufficient guidance for the development of innovations.  More importantly there should be an enabling environment for deliberative public processes with decision-making powers that will guide policies and force action to remedy and stop underlying causes that continue to worsen current crisis and to find real and long-term solutions, including change of practices and type of interventions.  A technical solution approach is very limited in its reach and possibilities. | |
|  | 36 | REPLACE: applications ~~is~~ **would be** needed  This whole issue needs much further discussion and is not mature enough to be covered here in this angle. | |
|  | 42 onward | Include ‘horizon scanning’ | |
| 13 | 3-7 | How about products? | |
| 13 | 4 | RREPLACE: ~~conventional~~ **first generation** LMO (“conventional LMO” is a misnomer) | |
| 13 | 6 | “concerted effort from all stakeholders”. The processes available are not balanced and there are vast power discrepancies as well as resource discrepancies. Unless these are properly balanced any efforts will be largely in vain to achieve an agreeable outcome. | |
| 13 | 32 | “by the large number of near market applications” please be clear about numbers. Large number does not mean anything. | |
| 13 | 34/35 | “Moreover, as synthetic biology will continue to grow in relevance and importance due to the opportunities that it offers towards solving global challenges...” This, as discussed in the beginning, is an unsubstantiated claim and assumption. Without proper and reliable broad spectrum multidisciplinary benefit analysis - which is at present not possible as there are no agreed methodologies nor experience nor agreed societal values or requirements and framework - and given the speculative nature of many of the claims, such a statement is not helpful in this context, nor should it be the basis for policy suggestions and further actions. | |
| 13 | 40 | Table | |
|  | General comment | I am surprised that all the listed developments are categorised as synthetic biology. Further I find the categories unclear, both for “intended use” as well as what is understood to be “advanced development” and what is “commercially available”.  There should be extra columns to show if an organism or product for intended containment could survive or spread into the environment, commercially available does needs to distinguish between what is actually being used and on the market or what is simply not being taken up or no longer taken up.  Advanced development needs the clearest definition and from my perspective would include that field tests or equivalent product tests have been carried out, and that it is clearly beyond the actual initial research stage. | |
| 14 | bottom | Unmanaged or wild settings: this should also include algae in the research column and gene drive mosquitoes in the Advanced development column | |
| 16 | 11-13 | Feels that is too limited. How about interventions made? | |
| 16 | 25 | DELETE: Potential impacts ~~of~~ on the | |
| 16 | 26-27 | Re case by case: This notion as presented here is counter to discussions and deliberations over the year on the issue, and is also counter the understanding of providing guidance regarding specific blocks/or categories of LMOs, for example. A case by case is for the final stage of individual applications to the regulator but initially it is too narrow and will not provide any possibility for guidance or understanding which expertise might be required. It is desirable to categorise blocks of ‘applications’ (in the widest sense) and to undertake initial assessments and sufficiency of methodology, guidance and understanding.  COMMENT: here - as mentioned previously - is an example of confusion of terms. For regulators (especially in the EU) and “application” is the submission of a dossier to the authorities in request of gaining approval. | |
|  | 43 & 44 | “supporting” Technologies - see Comment page 10 line 10 | |
| 17 | 3 | Testing of “biological” systems. Which systems? Limited systems? Specific systems? | |
|  | 3 | Reference wrong or interpretation wrong. E&W do not cover 'in silico testing of biological systems' - but rather point to the limitations of in silico predictions. Please clarify what is meant here by biological systems (which ones? how complex?) and how "testing" is being performed and for what? otherwise say "and to a limited extend in silico predictions". (this would go along with E&W, 2013). | |
| 17 | 6 | “longer lengths of DNA” - its not longer lengths as such, but just that more DNA can be covered/sequenced in shorter time | |
| 17 | 6 | Consider replacing ‘often’ with ‘commonly’, as that is what is mostly done with current next generation sequencing. | |
| 17 | 7 | COMMENT: It is however increasingly understood and reported on in recent publications that there are shortcomings to high throughput whole genome sequencing and checking against reference libraries: it is vulnerable to failing to see/identify larger chromosomal alterations, such as translocations, duplications, inversions and even some scrambling. | |
| 17 | 8 | Please correct 2017 to 2016 and adjust text. According to my understanding of Shapira: The search was for the time between 2000 & 2015, the authors identified 8064 papers, though perhaps not all were counted in the final outcome (please check yourselves) - and the publications importantly also cover  patents applications. | |
| 17 | 9 | “since 1980, ...” COMMENT: is that between 1980 and 2019? and how come between 1980 & 2000, where Synbio really wasn't a topic or an approach. Please clarify. | |
| 17 | 22-23 | Agreed, but also there seem to be divergent views on why calling it “supporting” technologies (please see comments for page 10 line 10) | |
| 18 | 27-29 | ADD or REPLACE: “....(TALEN), and CRISPR**-Cas9 (or alike)**. These ~~techniques~~ **site directed nucleases** can be engineered to bind to DNA sequences 27 in specific manners (Carroll, 2013; Gaj et al., 2016; Lienert et al., 2014). Approaches using SDNs and ODM 28 are applied to introduce random (SDN-1) or ~~directed~~  **specific or pre-designed** sequence ...” | |
| 18 | 30 | Please ADD & ALTER, as otherwise a wrong or misleading impression is given “These approaches do **mostly but** not ~~necessarily~~ **always** require the stable...” | |
| 18 | 33 | ADD: “..**eventually** degraded by ....” | |
| 18 | 34 | ADD: “..transgene **(which is commonly done for plants, as well as in many animal settings)** or introduced...” | |
| 18 | 37 | Just a grammatical correction: “... final host organism ~~and~~ are heritable..” | |
| 18 | 41 | “improved” is a specific point of view, which may be different from a biodiversity point of view or agro-performance or food-web point of view. Please ALTER: “ ...bean with ~~improved~~ **altered** oil quality **or composition** ....” | |
| 18 | 46 | ADD: “..... almost all **genome editing** studies and ....” | |
| 18 | 47 | ALTERATION: “ ~~..... have been addressed by genome editing~~.” Replace with to enhance clarity: “**are being investigated or addressed by genome editing research**.” | |
| 18 | 48 | “applications”. What please is meant by 'applications' here? Do you mean its use in laboratory research? General application of a technology? Submissions to regulators for approval or field testing? please explain/define, as 'application' can be understood to be a final product that is being tested for marketing, or it can be a certain category, such as herbicide tolerance. | |
| 18 | 48 | Please ADD at the end to add clarity and better understanding “.... has increased exponentially worldwide, **often in aid to understand gene functions and related traits, as well as to improve the methodologies and increase efficiency and reduce off-target effects (for plants see Eckerstorfer et al. 2019)**. | |
| 18 | 49 | ALTER: “...... ~~and~~ **. This** has led to advances in plant and animal **genetic studies and** engineering and ...... “ | |
| 19 | 2-3 | I neither understand this sentence nor does it seem to be fitting at this place. | |
| 19 | 4-5 | “CRISPR-Cas technology is having impacts in agriculture, especially in increasing plant yield, quality, disease resistance and herbicide resistance, breeding and accelerated domestication (Zhu et al., 2020).”  As stated above, this is a wish-list but not a reality. ODM herbicide tolerance has been achieved, the benefits though of which are being argued with regards to impacts on biodiversity due to herbicide applications. It is indeed one of the easiest traits and most popular traits to genetically modify/engineer and to bring to market. | |
| 19 | 6 | “... it is now possible to ...” This sentence is said much to general, whilst in fact these are first attempts in a direction that is not yet clear if it works the way some hope it might. Thus caution and restrain in the message is required. | |
| 19 | 4-9  General comment | This section is portrayed too positive and optimistic as if all of this is doable, and is just around the corner. Yet for example de novo domestication of plants has a spectrum of serious risks (including for food safety), as well as hurdles, which is being discussed in discussions elsewhere and should perhaps also have been included here. Adding to the hype will neither help the debate, nor finding solutions to achieve resilient and biodiversity supportive farming systems. | |
| 19 | 9-10 | Please ALTER to give the full picture: “CRISPR tools can **- amongst other methodologies and techniques -** also facilitate ~~the precise control of plant chromosomal recombination~~ facilitate 'controlled recombination' by inducing chromosomal cross-overs where they commonly do not occur (Taagen et al., 2020). ~~thereby~~ “**Whilst this is seen by some as** unlocking otherwise inaccessible genetic diversity**, it is seen by others as overriding the plants protective mechanisms, for example by knocking out the suppression genes for cross-overs. The unintended consequences of this are not known, as the whole system is still too little understood, and control is difficult.”** | |
| 19 | 14-15 | - the failure to go through to the market may in part be due to unintended effects due to the knockout of genes which may lead to the intended trait but also to other consequences, e.g. due to pleiotropic effects and altered gene regulation and feedback loops. | |
| 19 | 16 | “and may soon appear commercially” - All of these will still require risk assessment, and experience shows that obtaining a specific trait does not necessarily make it an agronomic successful plant or a biodiversity friendly plant. | |
| 19 | 27-28 | This statement or definition is problematic, as selfish genetic elements -such as transposons- should not be seen in the same light as gene drives, despite recent attempts to change the terminology and alter the perception gene drives. This is not the place to add to the controversy, in particular as SGE have often a role on the evolutionary scale, in particular with regards to speciation (Critical Scientists Switzerland et al., 2019). Please simply just define engineered gene drives, as those are clearly distinct in function and purpose from natural occurring phenomena. | |
| 19 | 29 | Again, Wolbachia should not be viewed or treated as a natural “gene drive system”, as it attempts to blur the boundaries, which is unhelpful for scientific debate, clarity, risk assessment and risk perception. If this document wants to elaborate and look at the different sides of arguments and debate, then this should be done carefully. Yet to portray matters from one specific point of view only, namely the view of gene drive developers, then this is not suitable for this CBD update report. | |
| 19 | .... |  | |
| 19 |  | **FURTHER comments are available and will be sent separately.** | |
| 19 | 29 | Re “natural gene drive system” - the term was also not used in the 2015 technical series version. | |
| 19 | 30-31 | “The potential application of these natural gene drive systems to suppress populations **of** insects has been studied in field trials since the 1960s.” This is not correct. This statement implies a steady stream of field trial study since the 1960 of insect with so-called ‘natural gene drives’ in an attempt to apply these for the suppression of insect populations.  Whist the existence of male bias sex-distortion in mosquitoes was reported in the 1960 and attempts were made to understand its molecular mechanism (which is linked to a specific Y-chromosome but was and still is not fully understood), it became evident that counter measures arose and were active to rebalance the sex ratio. This was well elaborated, and based on the “Fisher’s principle” of sex-ratio equilibrium, by Hamilton (1967), who suggested for example the occurrence of counter mutations as a response mechanism. However, this cannot be equated with the statement made in line 30-31, nor can later investigations and proposals of mechanisms (e.g. Davis et al. 2001).  Hamilton WD. Extraordinary sex ratios. A sex-ratio theory for sex linkage and inbreeding has new implications in cytogenetics and entomology. Science. 1967 Apr 28; 156(3774):477-88. doi: 10.1126/science.156.3774.477. | |
|  | 42 & 43 | “ These CRISPR gene drives are efficient tools to spread...” ....” CRISPR gene drive will produce offspring that all carry the gene drive....”  This statement expresses and over-confidence in the capacities, efficiency, efficacy and reliability of CRISPR/Cas-based gene drives that is not warranted and not supported by the scientific findings. The build-up of resistance has been a hurdle since the beginning, which was overcome in a particular study and design by using a very specific target gene, namely the doublesex (Kyrou et al. 2018). The use of CRISPR-Cas in other gene drives has proven less reliable and it is a serious concern within the gene drive developer community, who is working on overcoming these problems through new designs an approaches. It is exactly the fact that CRISPR/Cas based gene drives are not 100% reliable over time and space that give rise to risks on a multitude of different scenarios. | |
| 20 | 6 | “consequently”. This is not correct, as due to mutations resistance can arise (as shown in numerous papers. Furthermore “real world/life” factors like alteration of temperature or impact of stressors have been shown to influence the activity of CRISPR/Cas and makes them less reliable than when extrapolating from constant laboratory conditions. | |
| 20 | 10 | ADD - Word missing: “... present **in** almost ....” | |
| 20 | 18 | ADD “...repression **of a gene**.” | |
| 20 | 25 | “ ... or avoid food waste” ?? this addition/statement does not fit here or in this form | |
| 20 | 31-32 | ALTERATION & DELETE “.... dsRNA molecules ~~with potentially fewer or negligible~~  **also in the hope of ultimately affecting fewer** off-target effects .....”  There is too little data, including sequence data and experimental data available to make a statement as originally presented here.  Concerning “or negligible”: DELETE, as this is a premature statement. What makes an off-target effect negligible is down to risk assessment, and cannot be assumed in a general statement. | |
|  | 34-42 | Please make adjust to make sure that these are particular pieces of research that cannot make a general statement, neither for wider application nor for further development. | |
|  | 41-42 | This comes across too certain or strong, since this is a field of ongoing work, whith much left to understand and to learn, including the unexpected and the drawbacks (as also pointed out by Basso et al. 2019) | |
| 29 | 12 | “.... provided an unprecedented toolbox for tailoring organisms for new applications ..”  This approach of presentation is problematic, as it clearly presents from the perspective of the technologist and developer perceiving anything in the natural world as targets, objects, components, but not as part of elaborate networks and ecosystems or as organisms in their own capacity. This jars to a large extent with the perspective of those active in the protection and conservation as well as sustainable use of biodiversity. I suggest to rephrase this sentence as well as to adjust the tone and perspective chosen in this section. | |
|  | 14 | DELETE & ALTER “...the ~~incredibly~~ large and diverse range of products that are **being researched or are under development** ~~being developed~~ ....” | |
| 29 | 17-30 | whilst this categorising gives a rough guide, it should also be spelled out that intended receiving environment might be different from actually receiving environment - as we have learned for example with plastics and micro-plastics; wind-drift and water are often underestimated in their capacity to transport compounds as well as small organisms - this would for example be an important point for dsRNA spray or applications.  Furthermore: some applications will also intentionally (as well as unintentionally) span across the boundaries of these categories, e.g. some gene drive applications.  Please see also comment for the table, page 13, line 40, general comment. | |
| 29 | 32 | DELETE : “.... tested in ~~confined~~ field trials), ....” This is not CBD/CPB language, please just state "field trials". If necessary, add footnote that some regulatory systems such as countries xyz will use the term 'confined field trials', by which the mean ...abc... . | |
| 29 | 39 | As elaborated for the table, this section should include “ *Engineered gene drives in mosquito for potential control of vector-borne diseases”* from page 32, line 5 onwards. This is because there is no hard border and the target species is the wild species and is possibly in exchange with other members and populations in wild settings. | |
| 30 | 35 | ADD: “... Cas9 was developed for mice**, though with limited success and exposing limitations of CRISPR/Cas-based gene drives in mammals**. | |
| 30 | 37 | REPLACE: “.... to ~~heritably immunise~~ **engineer immunity** | |
| 30 | 41 | ALTER heading: The heading should read**: Applications aimed to improve** ..... | |
| 30 | General comment | Please consider re-writing the text, esp. the 1st paragraph, in a way that it is clear that this is research and that there are initial findings or ideas, and that broader implications, limitations and drawbacks have not yet been considered or explored. | |
| 30 | 42 | “Synthetic biology is currently being applied to conservation (Piaggio ....”  Saying in is being “applied” gives the wrong impression that it is being used in situ, in the field, in practical terms. Yet this is about research, so the sentence needs adjusting to avoid confusion as well as concern. | |
| 30 | 42 | “In ocean ecosystems ...” - again, this is research, but it reads as if it is being applied/used in the actual ocean ecosystems. | |
| 31 | 17 | “mutation” - These should be referred to as "modifications"  and shouldn't this be plural? as its two genes involved? | |
| 31 | 27 | This should be moved to 'advanced development' as these insects - and in particular the RIDL-mosquitoes - are still in the testing phase and trialled in different environments with varying results. Some of the ones listed have not even been field trialled yet, thus may not even fall under "advanced development".  In fact, current section 3.2.2.d (page 32, lines 20-33) are dealing with this. | |
| 31 | 28 | I suggest to change the beginning and instead say: “ Insects have been genetically [engineered][modified] to contain | |
| 31 | 28 | ADD: “ ..... results in **the death at the larval stage when modified males mated with wild-type females. This in turn has** ...” | |
| 31 | 29 | “pests” - it does not deem quite appropriate here or accurate to consider all the species as such as pests. I suggest rephrasing. | |
| 31 | 34 | I suggest to have separate headings (and paragraphs) for genome edited plants and genome edited animals.  Please clarify in each case what you understand 'advanced development' to be. It is my understanding from the scientific literature that most research reported on crop traits is either investigating the mechanism and the genetic basis and interactions of these traits, or they are improving or testing the technologies and using known genes as targets. (e.g. Eckerstorfer et al. 2019) | |
| 31 | 36 | “ ... are already under development.”  "under development" is not "under advanced development" - under investigation? And then it should possibly be listed under research.  Please be clear and be sure which ones are indeed under advanced development (and what that entails) - and which ones are in research. | |
| 31 | 36 | “A yield-improved maize ...”  This is giving no information about the modification, nor does it state how the particular crop has performed under different conditions and over time. The authors of this report need to be certain that what they report is correct and clearr, as it is a document that policy makers will have to rely upon.  A claimed trait of enhanced yield needs thorough testing under various conditions - including stress conditions - to verify such enhanced yield. It equally has to be tested for the presence of unintended and unwanted traits, as yield enhancement is not a singular trait, further more, it frequently makes plants more vulnerable to disease or pest attack. | |
| 31 | 40 | “...reported 67 animal examples that are being developed by genome editing”  It has to be clear that these are being genetically modified using genome editing.  Please be certain that each of the 67 animals you refer to are in ‘advanced development intended for marketing’. As with first generation genetic engineering - it is important to differentiate between actual reality, explorative research and a wish list (with explorative research including some initial results, but without the safety assessment and long-term performance assessment.  As generally known in the animal genetic modification community, it is unfortunate that funding commonly is only provided if one is to officially "develop" something to a purpose. Consequently the funding applications as well as the later reporting in scientific papers will always have to frame it in this particular way, namely as a success towards a specific goal. Yet this CBD report should refrain from following such patterns and clearly and cleanly delineate what is real and what is not.  I have not investigated the list of the 67 animal examples - I rely on the author of this report for doing so. | |
| 32 | 6-8 | This would only be the case for gene drives that are intended to alter or add particular traits, yet CRISPR-Cas based homing gene drives only require the genetic information (or gene set) for a CRISPR-Cas targeting an haplo-sufficient essential gene (e.g male or female specific) (Willis & Burt 2021), | |
| 32 | 9 | It is not appropriate to elaborate on specific organisations, companies or consortia, unless this would be done in every case and was wanted as part of the information of the report. | |
| 32 | 20 | To our understanding this was not designed or developed as a ‘bio-containment’ system but as an insect suppression system via genetically engineered suppressible sterility. “Bio-containment system” gives a different expectation/impression. It would thus be good to alter the heading accordingly and also ADD “(Oxitec)” at the very end to help clarity and ease of recognition.  Please also clarify for the reader - unless of course this is not the case - that this is the same technology and the same experimental insects as listed on page 31, line 27-32. If this should not be the case however, again, please clarify and what the difference would be. | |
| 32 | 36-37 | I suggest to include further information and alter the sentence to read:  Particle bombardment resulted in transgenic sorghum lines where the grain showed an increased content of easily digestible proteins in small field trials. | |
| 32 | 38 | Change “achievements” for “**results**” | |
| 32 | 39 | Again, as in other cases, is this research done to take these plants/crops further towards marketing and has this already advanced considerably on this route including ? or is it research testing possibilities and investigating traits? Please clarify the extent of development and whether marketing will be sought.  Heading: should say: “to potentially/possibly enhance...”, as it is not clear what the side effects and drawbacks are of this modification (knockout), whether it makes the plant more vulnerable to biotic or abiotic stresses, alters composition, nutrient uptake or processing, etc. Strigolactone plays an important role not only in morphology but is also involved in semiochemical communication, hence it would be good to provide some environmental research data to that effect.  Strigolactones (as root exudates) are part of communication systems (including triggering germination of the parasitic witchweed (striga), as observed in the push-pull agricultural system. Knocking out strigalactones is thus not just a matter of morphology, as suggested here. | |
| 34 | 9 | ADD: “..pest can **for example** be applied” | |
| 34 | 10 | DELETE: “...then ~~naturally~~ translocates the RNA...” The “naturally” is not only superfluous but it is also highly confusing as it seems to apply something special or specific, whilst it just is what an organisms does, like for example repair the DNA when its been cut with an endonuclease. | |
| 34 | 11 | ALTER/REPLACE “ ... ~~This~~  **The possibility of** transient modification | |
| 34 | 12 | ALTER/REPLACE “... has been ~~proven~~ **shown** in the....”; either “was shown” or “has been shown” ... It is important to not overstate or generalise findings and their meaning. | |
| 34 | 13 | REPLACE: “...... application of dsRNA ~~protects~~ **was able to protect** plants **in the specific experiments** from: aphid-mediated ....... “  As the observed protection is/was valid for the cases investigated but are not necessarily generally true or under different conditions, and as it is part of experimental research the better language would be as just detailed above. | |
| 34 | 17 | REPLACE: “Each example is ~~an important first step towards developing practical applications of this approach in crop protection~~ finding, **but more research is required, including into potential negative impacts of this technology and its use/application in agriculture or forestry, in particular on non-target organisms, on food-chains and food-webs.”** This section should alert the reader to the risks and potential negative impacts, as well as to uncertainties due to the lack of a full understanding. (and this should then be discussed fully later). | |
| 36 | 7 | REPLACE: “Novel ~~CRSIPR~~ **CRISPR associated** proteins ..” | |
| 36 | 20 | ***It would be appropriate to provide an introductory paragraph here and at the top of the research section to clarify, that*** the fact that particular developments or research is listed here does not mean that they will work, be applicable, be the best or appropriate solution, be safe or be sustainable. They are merely listed as an indication on what is being looked at by research groups in academic and business settings and thus enrich the knowledge and understanding. | |
| 38 | 21 | ADD paragraph - As already stated for page 36:  ***It would be appropriate to provide an introductory paragraph here and (and possibly at the top of previous research sections) to clarify, that*** the fact that particular developments or research is listed here does not mean that they will work, be applicable, be the best or appropriate solution, be safe or be sustainable. They are merely listed as an indication on what is being looked at by research groups in academic and business settings and thus enrich the knowledge and understanding. | |
| 39 | 2-3 | Please ALTER: “With the rapid rise in the design of synthetic engineered organisms in recent years, the opportunity to apply them to ecosystems and human health is expected to increase.”  Rapid rise? Why “opportunity”? - for whom? This first sentence unfortunately sounds somewhat like a sales pitch, which is most likely not intended. It also would not be a logical consequence that simply because synbio is applied to more or an increasing range of organisms in an effort to redesign them, that these organisms (or their products) would or should therefore increasingly be used in or on ecosystems. | |
| 39 | 3 | DELETE. Following on from above please delete “Therefore” “~~Therefore, c~~**C**ontinuous effort....” | |
| 40 | 30-34 | PLEASE HIGHLIGHT - and ADD to SUMMARY  This is an important paragraph and should therefore be highlighted in the layout, It should also be prominently included in the summary. | |
| 41 | 17 | “...(e.g. suppression engineered gene drives versus chemical control agents)”. This is an unjustified assumption as these methodologies are very distinct and giving rise to different impacts. Suppression gene drives may give rise to unintended modifications (due to the presence and activity of CRISPR/Cas, which will be triggered in each generation anew: off-target effects and near-target effects as well as mutations of the guide RNA that may result in resistance and unintended target sites) which in turn may result in unintended and unassessed traits. ......  It can thus result in the presence of an altered species. It can also result in the complete elimination of a whole species due to its self-multiplying spread, which chemical pesticides cannot do. Unless seriously investigated with good and reliable data sets gathered over time and space, comparisons between GDOs and pesticides are not helpful but rather misleading. | |
| 41 | 35 | This heading but and section is lacking ‘replacement’ (including niche replacement) and importantly also the rebound effect (as found in Singapore for example and as observed by others), where the suffering from malaria increases many-fold if Malaria had gone for some time and then has returned, also leading to an increased number of deaths and serious illness. | |
| 42 | 24 | Please ADD to the references: Critical Scientists Switzerland et al. 2019 | |
| 42 | 27 | DELETE: “.. with ~~genuine~~ potential ....... ” | |
| 42 | 28 | “unwanted” - by whom? Who decides? What are the consequences? | |
| 42 | 29 | REPLACE “particularly appealing” with “envisaged” | |
| 42 | 30 | ADD “ vertebrate extinctions **due to presence of invasive species, such as rodents** and w...” | |
| 42 | 30-31 | REPLACE & ADD: “... reached  ~~but can ensure that the impact is better contained geographically~~ **. The hope is that the impact of the release of LMOs containing gene drives can be better contained geographically and that the gene drive organism may not spread beyond the island setting**. However, **both here as well as** their use elsewhere”.  The use on islands also raises concerns in terms of potential spread - please see CSS et al. 2019, which you are quoting here. | |
| 42 | 35 | “ ...has stoked fears ..” This is an unfortunate choice of language. “ has given rise to serious concerns across .... that.... “ or something similar would be more appropriate. | |
| 42 | 36 | ADD : “ .... have **serious** unintended **and unpredicted** consequences for ecosystems, **biodiversity and human health**. | |
|  | 40-44 | This paragraph on its own is problematic and seems to forget crucial points that need rraising, reconcidering and adding.  For example: rebound effects, altered ability to transmit, higher virulence, niche replacement, etc (please see CSS et al. 2019). This should be added here, as potential negative health impacts are so far missing. This sentence and content is not presented in a helpful manner, but rather comes across as a lack of thoroughness and as an oversimplification.  Please also add the latest information on the new and 77% effective malaria vaccine called R21/Matrix-M (Datoo et al. 2021). Please do not mix up with the previous low efficacy RTS,S vaccine. The new vaccine, having been tried in Bukina Faso, meets the WHO requirements for effectiveness.  Please further make sure that the issue of access to healthcare is covered, as this is regarded as one of the main reasons for the continued prevalence of and suffering from Malaria (together with education and access to good nutrition).  Datoo MS, Natama MH, Somé A, Traoré O, Rouamba T, Bellamy D, Yameogo P, Valia D, Tegneri M, Ouedraogo F, Soma R, Sawadogo S, Sorgho F, Derra K, Rouamba E, Orindi B, Ramos Lopez F, Flaxman A, Cappuccini F, Kailath R, Elias S, Mukhopadhyay E, Noe A, Cairns M, Lawrie A, Roberts R, Valéa I, Sorgho H, Williams N, Glenn G, Fries L, Reimer J, Ewer KJ, Shaligram U, Hill AVS, Tinto H. Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. Lancet. 2021 May 15;397(10287):1809-1818. doi: 10.1016/S0140-6736(21)00943-0. Epub 2021 May 5. PMID: 33964223; PMCID: PMC8121760. | |
| 43 | 43-45 | ??? This sentence does not make real sense or feels out of context | |
| 44 | 2-4 | This is a very limited view that when examined will not hold up, as alteration of trait may change also behaviour and niche and thus bring about shifts | |
|  | 25 | Whilst the previous block was already largely in praise of benefits (instead of staying neutral), this is done here again. Just a headline like this gives a wrong signal, unless it was followed up by 'threatening/undermining agricultural performance and biodiversity"  In the absence of the ability to undertake robust benefit assessments (due to lack of agreed methodology and experience and data), and given that such benefit assessment would require to evaluate suggested benefits in comparison with other solutions and approaches and their deliverance of benefits, as well as  distinguishing between short-term and long-term benefit - in the absence of this potential benefits should not be equated with real benefits or the solution of choice.  Yet, even in the section concerning impacts, prevalence and priority is given to assumed benefits whist risks and potential serious negative impacts are being side-lined.  it is disappointing to see a CBD document with such bias and I hope that the final product will make more effort to understand and correctly portray the risks, and to do so in the right context.  The CBD has a history and track record of understanding, defining and implementing ecosystem approach based actions and solutions. It should not fall short here on its own obligations. | |
| 45 | 5-6 | This is not the case. | |
|  |  |  | |
|  |  |  | |
| 47 | 28 | Additionally - It should also be understood that those that are seeking rhino horn or other natural substances for particular types of medicine will not be satisfied by synthetically produced compounds and materials, as it is the actual “thing” derived from a particular organism that is associated with the power of the medicine, and less so the particular chemical composition, here reproduced in synthetic processes. | |
| 132 | 39-41 | It will also depend on risks associated with applications, on other strategies and solutions available to solve problems and underlying causes or to achieve benefits. | |
| 132 | 43-42 | We have to points here:  a) what are the authors meaning by "advance"? SybBio has advanced in which way? What new synbio knowledge or techniques have been added, or what is meant here?  b) And secondly, how can you tell it has been exponentially? Where is your assessment for this? The data? Or is simply accidentally picking up developers or business hopes and claims? | |
| 132 | 44 | “nearing commercial release”. When reading the sections on 'advanced development' most of these did not seem not near commercialisation - except maybe for applications in containment. Could you please clarify and adjust | |
| 133 | 8 | If this should be referring to the RIDL mosquitoes/insects, then the same mosquitoes were around in 2015 and had already been in open field trials since at least 2011 - and the same mosquitoes would be the ones that around now, also being field tested, now as part of pilot projects (Florida). According to Oxitec's website the current releases in Florida Key are part of a pilot project that will evaluate the effectiveness of the genetically modified male RIDL mosquitoes. | |
| 133 | 15 | ADD “the discussions **and deliberations** about” | |
| 133 | 22 | AAD “cause challenges **not only to their assessment, but also** to th.....” | |
| 133 | 24 | ADD “to **identify and** properly ... | |
| 133 | 24 | Add: after impacts. "This should include the expertise and views derived from different knowledge systems". (this was discussed during the last SBSTTA and is also in line with IPBES practices). | |
| 133 | 27-28 | “of additional tools 27 to complement this and other existing methodologies” - this is not clear | |
| 133 | 28 | ADD - “the **possible** inability”  Why “ potentially” ? | |
| 133 | 29 | “ the application”  perhaps replace with "some" or "an application"? As many will be detectable and identifiable, such as gene drives. As with applications of first generation of genetic modification, such as transgenics or cisgenics, detection also required the knowledge as of what to look for, and in cases of same constructs but different events, it also requires information about the surrounding DNA sequence. | |
| 133 | 30 | ADD at the very end: “**An international register, or internationally accessible national registers, of organsisms and products produced through synthetic biology would help greatly in such efforts**.” | |
| 134 | 5 | ADD: This is **reported to be** the case | |
| 134 | 10-12 | Not clear | |
| 134 | 29 | This sentence is a major claim and assumption that is not based on solid assessment and evaluation. | |
| 134 | 31 | ADD Significant **negative** impacts | |
| 135 | 12-15 | This is an inappropriate suggestion as final conclusion, and not a task for the CBD, nor for the CBD to put such suggestions forward.  Rather refer to the precautionary approach | |
|  |  |  | |

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