United States Department of State

Bureau of Oceans and International Environmental and Scientific Affairs
Washington, D.C. 20520

30 June 2021

Ms. Elizabeth Maruma Mrema
Executive Secretary
Convention on Biological Diversity
413 Saint-Jacques Street, Suite 800
Montreal, Quebec, Canada H2Y 1N9

Dear Ms. Mrema:

The United States appreciates the invitation to provide input in response to the Secretariat's Notification No. 2021-031 regarding peer review of the technical series on synthetic biology.

We are pleased to have the opportunity to share the attached views and information and thank you for your consideration of this contribution.

Sincerely,

Barbara M. De Rosa-Joynt
Division Chief for Biodiversity
U.S. National Focal Point for the
Convention on Biological Diversity

Attachment: U.S. peer review comments on the technical series on synthetic biology.

UNITED STATES PEER REVIEW COMMENTS
TECHNICAL SERIES ON SYNTHETIC BIOLOGY

Contact information	
Surname:	Shinen
Given Name:	Jennifer
Government	United States
(if applicable):	
Organization:	U.S. Department of State
E-mail:	shinenjl@state.gov

Comments on the Technical Series on Synthetic Biology

Page #	**Line #**	**Comment**
0	0	Passive voice and vague language is found throughout the document to support rationale for taking action on specific topics (e.g., "it has been recently suggested that decision-makers may need formal and quantitative studies on potential economic impacts of handling" [pg 51, line 15]; "Questions of synthetic biology's impact on attitudes" [pg 52, line 44]; "Synthetic biology is seen by some" [pg 53, line 8]). To avoid confusion, we recommend that these instances be revised to provide clear, unambiguous support for the topic with appropriate references included.
0	0	Citations are missing throughout the document, and we recommend including citations for many of the assertions made as this will strengthen and substantiate the text by providing evidence of the facts underpinning the statement.
0	0	The document interchangeably uses "applications" and "products" throughout the text. Applications can include a great many individual products. We recommend that terms be used correctly and consistently to foster clarity.
0	0	We consider that the document is inconsistent in its description of regulation in relation to synthetic biology and we recommend that it be updated to reflect that regulation only applies to applications of synthetic biology, rather than the technology itself.
0	0	"Genome editing" is scientifically accurate and the established term of art by many international bodies, both research and regulatory. We suggest consistent use of this term in lieu of "gene editing". Genomes are targeted for editing, with the goal of changing gene function.

8	9	We suggest clarifying the text below to indicate whether there are synthetic biology techniques that are *not* ever used in applications of genetic engineering. If so, request that these techniques be included here or later sections. "Synthetic biology relies on a suite of supporting technologies and tools, some of which are also used in genetic engineering."
8	13-15	Suggested text edits in red below. CRISPR is one technique in the suite of genome editing tools and we consider that it does not need to be specifically highlighted. Genome editing is used to introduce traits into agricultural products, which is separate and distinct from the technology itself. "Particularly, genome editing tools can be used to~~CRISPR-Cas technology is having~~ impact~~s in~~ agriculture, especially by introducing traits that increase~~ing~~ plant yield, quality, disease resistance and herbicide resistance, breeding, and accelerated domestication."
10	15-16	We recommend including citations for this statement: "Moreover, technologies such as engineered gene drives can now potentially be applied to a wide variety of organisms as a tool to spread traits throughout a population."
10	19	We are not aware of a commercially viable engineered gene drive on the market to date. We recommend including a citation for the following statement or the following insertion: "Amongst each of these categories, several synthetic biology products are being commercialised, or are in a research and development stage."
10	25-28	We recommend that the following statement be edited and clarified. It is not clear to us who is meant when the text indicates "Seen". We note that evaluation of non-science based factors are not an obligation of the CBD or its protocols. "Therefore, a science-based assessment of any potential impact is seen by some Parties as part of a wider decision-making activity; ~~one that~~ some Parties may be interested in considering ~~evaluates~~ ~~such~~ economic, political, moral, and ethical concerns ~~alongside a scientific analysis~~ of the expected or potential changes that would result from using technology. Such considerations should be conducted in a manner that is consistent with other international obligations."
10	31-32	We recommend the following edit: " this is bringing opportunities and challenges to building consensus on how they are to be ~~regulated~~ considered"
10	33-35	We recommend the following edit, to reflect that many countries are using approaches other than "regulation" to address these products:

		"At a national and regional levels, ~~regulatory~~ policy frameworks are developing at different rates and with differing perspectives with respect to synthetic biology governance."
10	38	We are not clear what the use of the word "laws" in the following phrase is intended to capture and we recommend the following edit to enhance the clarity: "Currently, the governance of synthetic biology is supported by a range of international ~~laws~~ obligations, processes, and initiatives,
10-11	45-2	We do not believe that the assertion that "international laws, processes and initiatives" are ill-equipped is factual and we recommend that this part of the sentence be deleted: "~~Enhanced regulatory oversight~~ Further discussion addressing these dimensions ~~appears~~ may be desirable to promote public trust and acceptance, ~~however, the international laws, processes and initiatives analysed appear ill-equipped to address several of these dimensions.~~ With over a decade of substantive decision-making addressing synthetic biology, the Convention on Biological Diversity has emerged as an important international forum currently deliberating the potential impacts of synthetic biology ~~and its regulation~~, particularly as they relate to biodiversity and biosafety. The Cartagena Protocol on Biosafety provides the venue for Parties to further discuss issues related to biosafety and potential socioeconomic considerations of products."
10	46	We recommend inclusion of references to support the statement below both here and when mentioned elsewhere in the document. At present, we know of no gene-drive modified organisms that are in the pipeline and could reach the market in the next few years. "It is expected that some other genome edited organisms and potentially those containing engineered gene drives could reach the market in a few years."
11	3-10	We do not believe the following statement is accurate and we believe it could usefully be clarified to ensure it is accurate. Not all countries or Parties agree that there is a "recognised need to better coordinate" to consider these issues. In fact, the international community has a strong history of coordination on considering products across multiple fora—not just the CBD. We are not clear what the phrase "elements of social justice" is intended to capture. We believe this could usefully be clarified.

		We are also unclear what is the phrase "associated geopolitical challenges" is intended to reference, and we consider that this could likewise benefit from some clarity in the phrasing. There is a recognised ~~need to first better integrate and coordinate~~ opportunity to continue to discuss governance of synthetic biology, and secondly, for some products of synthetic biology, to consider whether it is necessary to expand the focus of governance beyond the focus on biosafety, human health and the environment to a more holistic approach that also encompasses social impact and ethical principles, ~~and elements of social justice~~, in accordance with international obligations and national circumstances. To avoid unintended irreversible environmental damage ~~and associated geopolitical challenges~~, innovative research guidelines, governance methods, integration with social sciences, and engagement with communities ~~are~~ may be needed for some products of synthetic biology. As we think about advancing synthetic biology into the future, the opportunity and challenge is integrating the scientific freedom that allows research and product development to move ahead while acting responsibly and in a manner that embraces ethical, legal, and larger societal values.
11	34-35	We consider that this sentence is alarmist and factually incorrect since no technology is boundless. As a result, we recommend deletion or significant revisions to improve the tone and accuracy of the statement. "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."
11	44-48	We have made suggested text edits in red below. As currently written, this statement implies that existing risk assessment and management strategies across the board are not fit for use and need to be revised. We consider that stakeholders must also be provided essential information as to the benefits of the associated products/applications. "Regulatory decision-making on activities involving synthetic biology products requires more than just a crucially important assessment of characterised risks, potential benefits, and potential prescribed risk management strategies, but should also include ~~as~~ the degree to which a risk is acceptable ~~is a social construct, as are the guiding policy goals. Neither can be determined purely scientifically and should instead be informed~~ through consultation with a broad set of stakeholders, including the populations likely to be impacted most."
12	43	We recommend the inclusion of more support for this statement here and elsewhere in the document. We also recommend that evidence be provided to support the supposition that nations will not be able to adequately assess products as they are introduced into the market. We are not clear whether the authors are

		suggesting the creation of domestic or international mechanisms that consistently assess the field of potential products beyond what are currently in place, and this language could usefully be amended to enhance the clarity of the sentence. "Considering the fast pace of development of synthetic biology, and the challenge for regulatory regimes to cope with potential new applications, an early screening of what is under research and development and their commercialisation perspectives will be critical in providing timely information for countries and organisations to react and adapt if necessary."
12	47	We have made suggested text edits in red below. We consider that the rationale behind this statement is unclear. The adoption of the term "synthetic biology" after the establishment of regulatory process does not necessitate that those processes require updating. Our suggested edits reflect that new tools have come into use and that there are new *products/applications* that may require updated regulatory mechanisms to assess. "14. Many~~ost~~ regulatory mechanisms were developed before some tools that enable~~the term~~ synthetic biology became widely used and these mechanisms may need updating to address some applications of synthetic biology."
13	6-8	We recommend inclusion of the text insertion below in red: Thus, the discussions on potential impacts have been informed mostly by previous experience with LMOs and associated benefits and concerns.
13	9-10	We suggest inclusion of the edits shown in red below. "International governance and regulation" may inaccurately imply that a single international body/coherent structure is currently in place or necessary for SynBio applications. Our recommended edits reflect that governance and regulatory bodies are supported at the national level "~~Intern~~National governance, ~~and~~ regulation, and use of applications of ~~associated with~~ synthetic biology is complex and would benefit from a coordinated and cooperative approach."
13	11-26	We consider that this entire paragraph is also alarmist and factually incorrect. We recommend the inclusion of citations and significant revision.
14	27-38	We believe that this section would benefit from the addition of a factual sentence, noting the cost and burden overly restrictive evaluation of products may have on the ability for synthetic biology to live up to its perceived potential. We recommend the addition of text along the following lines: "The regulation and evaluation of synthetic biology products should be conducted in a manner that is risk-proportionate. Science- and risk-based assessments can support the streamlined commercialization of safe products. The incorporation of

		other factors into decision making processes should be done in a manner that is consistent with international obligations and not at odds with the findings of a science-based risk assessment. Parties should strive to avoid inhibiting or slowing the commercialization of products that could contribute to the goals of the Convention and its protocols."
42	17-24	We recommend deletion or clarification for the statements below. In the context of the section, the release of genome-edited or gene-drive modified organisms is meant to control or suppress a species population within a region, which nullifies the concerns of the statements below. IAS management applications are not applicable to native species populations. If the text is retained, suggested edits are shown in red below. "It is therefore possible that under certain circumstances, conservation gains from these uses could be offset or even outweighed by associated conservation losses elsewhere, for example if the target species is native or performs an essential role in community structure and/or ecosystem dynamics (Redford et al., 2019)). Further, depending on the type and scale of the modification, IAS management synthetic biology applications ~~gene-edited organisms~~ released into the environment for instance, could also result in unwanted impacts on biodiversity, including off-target mutations, evolutionary resistance, ecological disturbance and extinctions; each of which have triggered a heated discussion regarding their environmental impacts and regulatory oversight (Esvelt et al., 2014; Kofler et al., 2018; Romeis et al., 2020)."
42	25-26	We suggested the text edits in red below to reflect that the technology used to develop gene drive-modified organisms is not relevant. We recommend that this be reflected throughout the document. If the authors believe that there is an appreciable difference between CRIPSR and non-CRISPR gene drive-modified organisms, we recommend that this be explicitly discussed. "Engineered gene drive systems~~, notably CRISPR–Cas9 gene drives,~~ have recently emerged with potential applications not only in conservation but also in public health and agriculture (López Del Amo et al., 2020)."
43	4-8	We recommend deletion of this statement. Applications of many technologies may have ancillary, downstream effects on biodiversity that are completely unrelated to the original application and sets an unwarranted precedent that evaluates decreased public health risks with increase biodiversity conservation risks.

		"~~Further, although not specific to synthetic biology approaches, the reduction or elimination of human malaria from 6 geographical areas may lead to demographic and land-use changes, potentially impacting biodiversity conservation (Redford et al. 2019).~~"
45	11-16	We recommend that these statements be deleted. As described in lines 5-11, off-target changes to the genome are noted to occur during conventional breeding processes at rates similar to or below that of genome-editing techniques and that these changes can be effectively removed through back-crossing and that genome-editing does not lead to enhanced risk in comparison to conventional methods. "~~Those off-target changes that remain may lead to phenotypic effects affecting the properties of the modified organism (European Commission High Level Group of Scientific Advisors, 2017), and have the potential to ultimately lead to alterations of population characteristics, especially when spread amongst individuals via gene transfer. This may ultimately lead to unintended or unexpected consequences during interactions with associated species or populations in the surrounding environment.~~"
46	29-30	We suggest the text edits in red below to reflect that these concerns are linked to arable land usage derived from first-generation biomass applications. We note that biomass applications not associated with arable land use do not have the same implications. "Potential negative impacts could result from the increased utilisation of biomass derived from first generation synthetic biology applications that require arable land."
47	23-25	We recommend that further information be provided to clarify how replacement of natural products with synbio products would disrupt in situ conservation projects. "However, the situation is a little more nuanced than originally expected. For example, the replacement of 23 natural products with products resulting from synthetic biology could lessen the pressure on natural habitats 24 but could also disrupt in situ conservation projects."
48	15-18	As currently written, this statement implies that existing risk assessment and management strategies across the board are not fit for use and need to be revised and we recommend amending the sentence so it is focuses on facts and science. "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 (Johnson et 17 al., 2007)."

48	28-29	We recommend the addition of further information. The text does not make clear whether these emerging technologies and their applications are actively discussed by the research community, industry, and conservation societies. We recommend including more detail on the current gaps. Suggested text edits in red below. "As suggested by Oye et al. (2014), for applications of emerging technologies that affect the global commons, concepts and applications should be published in advance of construction, testing, and release."
48	35-39	Suggested text edits in red below. We note that "NBT" is not a well-defined term and is not used consistently throughout the document. "This same approach continues to be echoed, for example in a recent survey of experts (Lassoued et al., 2019) in which the majority indicated that the regulations for health and safety, followed by export markets, consumers, and the media play a major role in determining where and how newer genetic engineering technologies~~New Breeding Techniques~~ (Obukosia et al., 2020; Seyran & Craig, 2018), including genome editing, will be developed and used in agriculture."
50	12-15	Suggested text edits in red below to reflect that socioeconomic factors are not a component of a risk assessment. "Additionally, how IPLCs perceive nature, the unique way that they interact with it, and how this can be captured by the global regulatory governance and regulatory scheme, as well as in the risk analysis and management~~assessment~~ of impacts associated with synthetic biology, each present unique challenges that must be considered and overcome in relation to FPIC."
51	11-12	We recommend inclusion of a citation for this statement. "The different fundamental objectives of the international trade and 11 environmental regimes have led to conflicts in the regulatory measures taken to achieve these objectives."
51	15-19	We recommend increasing the clarity of these statements. "...impacts of handling" needs to be expanded to describe what is being handled – applications of synthetic biology? The text does not make clear how many studies are required and this could usefully be clarified, e.g., do we mean one study for each potential product? "Further, it has been recently suggested that decision-makers may need formal and quantitative studies on potential economic impacts of handling, for example genome-edited products, under different regulatory scenarios. Such studies would allow them to weigh the impact of different regulatory/policy-making options on

		the economy (considering trade, agro-industrial innovation 18 and productivity) (Whelan & Lema, 2017)."
51	19-21	The meaning of this statement, especially in relation to what is being indicated by "interpretative flexibility" is unclear and we suggest enhancing the clarity by revising the sentence. "A formal analysis of the trajectory or dynamics that the interpretative flexibility is taking may be useful to anticipate the social perception of these decisions (Duensing et al., 2018)."
52-53	44-49, 1-7	We consider that this paragraph is largely speculative and we did not see evidence to support the stated concerns. Most associated references are 8+ years old – with the continued use of synbio applications, is there more recent evidence to support that the speculated effects have been realized? "Questions of synthetic biology's impact on attitudes to biodiversity and conservation continue to be asked, especially around how synthetic biology will change public perceptions of what is natural, and if it will "challenge the ethical basis for conservation action" (Redford et al., 2013). It has been speculated that synthetic biology could "encourage an inaccurate model of biodiversity protection as maintaining an inventory of biological units" (Norton, 2010). Building on this, Redford et al. (2013) noted the increasing importance of ecosystem services in valuing biodiversity, and asked what will happen if ecosystems with synthesised elements are able to out-compete natural ecosystems, "delivering more services with less biodiversity". More recently, the debate about the potential use of synthetic biology with engineered gene drives have raised concerns not only about the potential impacts on biodiversity, but also ethical concerns about who will/should decide on the use of an application that could potentially spread across national borders. The scenario of a country approving the application and neighbouring country restricting its use is feasible and raises questions about governance and ethical issues that could be also related with the FPIC (see Section 7.1.2)."
53	11-13	We consider that this paragraph is largely speculative and we did not see evidence to support the stated concerns. Associated references are 10+ years old – with the continued use of synbio applications, is there more recent evidence to support that the speculated effects have been realized? "The application of intellectual property rights to synthetic biology, such as patents on DNA sequences or organisms resulting from synthetic biology, could restrict the global distribution of products and knowledge (ENCH, 2010; ICSWGSB, 2011; Schmidt, 2009)."
53	35-50	The implications of this paragraph are unclear and in our view it lacks a clear rationale that supports an outcome to the provided information. We recommend

		either greater clarification be provided regarding the point of the paragraph or its deletion from the document. "Common considerations have for instance included the ethical debate on whether to ban publications of dual use science discoveries and whether synthetic biologists are "playing God" (Boldt & Müller, 2008; Douglas & Savulescu, 2010; Kaebnick, 2009; The Royal Academy of Engineering, 2009). However, for some, "playing God" may not be regarded as problematical. One could argue that humans are the God species and should take control over natural processes in order to achieve human flourishing on this planet (Bovenkerk & Nijland, 2017). Thus, the role of human intervention in nature and natural processes, including this idea of naturalness have been raised as there could be a greater need to understand our values of nature, goals for conservation and the promise of biotechnology (Graeff et al., 2019). With the advent of new technologies, the biophysical influence of humans on nature could be more profound, having implications on biological evolution by controlling whole ecosystems and species (Graeff et al., 2019; Kaebnick, 2009). For example, editing a gene which has evolved over thousands of years could be viewed as a disruption to natural homeostasis (Šutković et al., 2020). Further, in the case of modifying genomes, the idea of integrity could be challenged with our understanding of how a genome constitutes an organism (Bovenkerk & Nijland, 2017). Another common consideration around the possibilities to either using this technology irresponsibly and cause harm, or not using it at all, which could also prove damaging to humans, our welfare, and our planet (Kofler et al., 2018)."
54	2-4	We have made suggested text edits in red below to reflect that there is broad support for this view, as well as specifically pinpointing the exact techniques. SynBio techniques are inconsistently associated with only genome editing techniques in the document and we recommend that this be reviewed and corrected within the text. "A number of researchers, policymakers, and regulators~~Some could~~ view the application of some genome-editing~~synthetic biology~~ techniques as analogous to selective breeding, especially in cases where species-specific function is not hampered (Bovenkerk & Nijland, 2017)."
54	17-20	We recommend inclusion of a reference for this statement. "The optimism expressed by some is not shared by all members of the conservation community, with some expressing deep concern that applications of synthetic biology may serve as "Trojan horses" for other "more questionable" applications."
54	23-25	We recommend that the statement below be reframed, supported with further evidence, or be deleted from the document, as it directly contradicts the previous

		sentence, which states that "policy debate to be grounded... impartial standards that are free from ideology or political bias..." "There therefore remains a large scope for society to be further involved in formative discussions concerning the acceptability or otherwise, and thus consequently the regulation of synthetic biology applications and products."
54	27-47	We consider that this paragraph could usefully be put into context with the relevant international instruments and standards that relate to hostile use of biological materials, such as the Bioweapons Convention. Without this appropriate context, in our view this section may imply that new approaches are necessary to address the listed concerns. "Bioterrorism, biological warfare and the construction of novel organisms designed to be hostile to human interests can all potentially be achieved through the malicious (or dual-) use of synthetic biology. Bioterrorists might, for example, create new pathogenic strains or organisms resistant to existing defences. Currently, it is possible to enhance the virulence of known pathogens with new traits that can contribute to their competence and resistance to existing treatments. For example, a novel type of avian flu virus with enhanced infectivity in mammalian animals may be created, and the H5N1 virus can be modified to evolve into a dangerous human virus (Herfst et al., 2012). It has even been suggested that pathogens might be engineered to attack only a particular genetic subset of a population (Garfinkel et al., 2007). Likewise, Mukunda et al. (2009) predicted that biological weapons customised to attack specific groups were highly likely to be developed in the long term (10 or more years), i.e. the period between the previous technical series document and this update. Although microbes are usually the main platform for the development of applications with malicious intent, plants are not immune to such approaches. It has been recently suggested 38 that criminals may exploit modern gene editing technologies to subject market GMOs to clandestine manipulation (or the malicious insertion of genetic modifications into ostensibly unmodified plants), raising the prospect not only of direct harm, but of the more likely effects in generating public concern, reputational harm of agricultural biotechnology companies, lawsuits, and increased import bans of certain plants or their derived products (Mueller, 2019). It has been further suggested that when (mis-)used, especially in combination with newer technologies such as engineered gene drives, virus-mediated methods, or in vitro evolution techniques, the effectiveness of current authentication and surveillance protocols may be overridden. Unfortunately, it is by no means clear that such abuses could be entirely eliminated, any more than they can be for other 'dual-use' technologies."
54	34-37	We consider that this paragraph is largely speculative and we did not see evidence to support the stated concerns. Associated references are 10+ years old – with the

		continued use of synbio applications, is there more recent evidence to support that the speculated effects have been realized? "Likewise, Mukunda et al. (2009) predicted that biological weapons customised to attack specific groups were highly likely to be developed in the long term (10 or more years), i.e. the period between the previous technical series document and this update."
56-57	47-48, 1	We are not clear what is meant by "completely new organism"? We recommend including more detail, as well as references to clarify the intent of this text. "While some might present less complexity and novelty compared to those produced by other methods or those coming for example from genetic engineering (i.e. LMOs), some might represent a completely new organism."
57	2-3	We suggest the text edits in red below to reflect that socioeconomic factors are not a component of a risk assessment. "Therefore, the adequacy of current methodologies for the environmental risk management and analysis ~~assessment~~ of synthetic biology products might depend on how their novelty and complexity is perceived (Wikmark et al., 2016)."
57	3-7	We suggest text edits in red below to reflect that the focus is on applications and not techniques. We recommend the inclusion of more information on the need for different forms and levels of oversight for different synbio applications. It would be useful to clarify which applications fall outside of current regulatory scopes. "Applications developed using d~~D~~ifferent methods and techniques of synthetic biology may need different forms and levels of oversight. Thus, any new risk assessments, cost-benefit analyses and regulations must flexibly encompass different applications~~, uses and products~~ (ETC Group, 2012)."
57	20-23	As currently written, this statement implies that existing risk assessment and management strategies across the board are not fit for use and need to be revised. We consider that stakeholders must also be provided essential information as to the benefits of the associated products/applications. "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 (Johnson et al., 2007)."
57	44-45	We suggest the text edits in red below to reflect that risk assessments cover applications and not technologies.

		"~~Here b~~Below some considerations regarding risk assessment for applications of three synthetic biology supporting technologies that have received considerable regulatory attention to date are presented."
58	17-20	We suggest the text edits in red below to reflect that this evaluation was performed in context of EC guidance. "As such, EFSA noted~~they are concerned~~ that EC regulations regarding~~the~~ molecular characterisation, environmental risk assessment and post-market environmental monitoring specifically of gene drive-engineered insects are insufficient and thus want further guidance to be developed which builds upon existing approaches (Naegeli et al., 2020)."
58	38-42	We recommend enhancement of clarity as to how engineered gene drive-modified organisms cannot be limited in time and space. We note that particularly when used to suppress species populations, these gene drive applications are self-limiting and remove themselves from the population and this consideration should be included in the discussion. "Unlike non-engineered gene drive organisms which can be limited in time and space and therefore provide data from small-scale tests that can be relevant to large-scale releases, the potential of engineered gene drive organisms to spread over large areas and landscapes, even from a limited release or well-isolated trials, means that risk assessors will need to consider models and forecasts in their assessments."
58	47-49	We recommend more information be provided about this statement. It is not clear to us how this significantly differs from products developed using transgenic or other genetic engineering approaches and amending the text could add clarity. "The latter captures concerns about for instance, genome editing allowing for modifications that would not otherwise naturally arise (African Centre for Biodiversity, 2020; Kawall et al., 2020)i."
59	9-10	We suggest the text edits in red below to reflect that the relevant techniques are genome editing techniques. "It's been argued that the current approach to risk assessment is not designed to detect unintended consequences that arise from ~~of~~ employing some ~~new breading techniques (i.e~~ genome editing techniques (~~;~~ Christ et al., 2018)."
59	12-14	We recommend more information be provided about this statement. It is not clear to us what the criticism is that has been applied and amending the text could add clarity.

		"However, the use of untargeted metabolites in the characterization of these crops has also been subject of criticism (Court of Justice of the European Union, 2018; Lassoued et al. 2019; Marchant, 2001)."
59	21-24	We suggest more information be provided about this statement. It is not clear to us how this significantly differs from products developed using transgenic or other genetic engineering approaches and amending the text could add clarity. "Characteristics of some genome editing applications, e.g., the small extent of genomic sequence change and their higher targeting efficiency, i.e., precision, cannot be considered an indication of safety per se, especially in relation to novel traits (Eckerstorfer, Dolezel, et al., 2019)."
59	48-49	We recommend clarification or deletion of the references to animal cloning methods. We note that currently, animal cloning predates and is not a genome editing technique. "However, a lack of scientific data on engineered animals, how animal systems respond to genome editing, mosaicism produced from animal cloning methods (e.g. somatic nuclear transfer)"
64	8-10	We recommend clarification or deletion of this sentence. As described in the rest of the paragraph (lines 10-16), single nucleotide changes to the genome are unlikely to have unintended/off-target effects. Therefore, if the single nucleotide change could have been achieved through conventional breeding methods and would not be detectable, what is the need for detection and identification? We recommend inclusion of a stronger rationale or deletion of the sentence. "This has important repercussions for the effective detection and identification of synthetic organisms, and especially for those authorised for international trade (currently plant-based commodities)."
64	17-45	Referring back to the previous comment (pg 64, lines 8-10), we consider that this section does not give appropriate consideration to the notion that single nucleotide changes in genome-edited organisms are unlikely to pose a greater risk than their conventional counterparts and would thus not need to be subject to detection and identification processes. We suggest reframing this section to focus on the detection and identification of genome-edited organisms that require greater regulatory scrutiny than their conventional counterparts.
66	25-27	We note that this statement is inaccurate and we recommend that it be revised to reflect that the USDA has a narrow exemption that applies to single base-pair substitutions. Please refer to and reference https://www.aphis.usda.gov/brs/fedregister/BRS_2020518.pdf.

		"Further, the USA Department of Agriculture announced that it has no plans to place additional regulations on genome-edited plants that could otherwise have been developed through traditional breeding prior to commercialisation."
67	11-12	We recommend clarification and inclusion of a reference or deletion. It is not clear from the text who has suggested that greater difficulties in detectability abrogates a need for regulation. We note that limitations in detection are not sufficient to remove regulatory requirements, as it is a question of risk rather than detection. "It has been argued that the detectability of genome edited products is technically more difficult compared to GMOs, and that therefore there is no point in having them regulated."
67	40-42	We suggest the text edits in red below to reflect that Parties can have their own flexible frameworks while staying within the objectives of the Protocol and that they *must* ensure that their processes follow their international agreements. "Therefore, Parties to the Protocol need to ensure an adequate level of protection in the field of the safe transfer, handling and use of LMOs ~~regulate such organisms according to the provisions of the Cartagena Protocol~~."
87	24-40	We believe this paragraph could usefully note the outcomes from the 2020 Risk Assessment and Risk Management AHTEG, which indicated that additional guidance for LM fish is not necessary at this time.
88	21-23	We recommend including more information to explain why containment facilities for LMOs would be insufficient for organisms developed using SynBio. "First, the International Civil Society Working Group on Synthetic Biology (ICSWGSB) (2011) argues that containment facilities that Parties consider to effectively contain LMOs may be unsuitable to contain organisms resulting from synthetic biology techniques."
89	1-5	We recommend including more information to explain why the domestic release application would be insufficient to adequately assess and manage the risk from releasing an LMO. "A third and more general issue, which is not limited to LMOs produced by synthetic biology, is that Parties could be faced with "regulatory arbitrage" − the practice of utilising more favourable laws in a jurisdiction to circumvent regulation elsewhere − if a laboratory imports a synthetic biology LMO for contained use and then makes a domestic application to release the synthetic biology LMO from containment (ICSWGSB 2011)."
90	32-34	We suggest the text edits in red below to reflect that this process is voluntary, using exact language from Article 26.

		"Article 26 of the Protocol addresses the extent to which Parties may take into account, consistent with their international obligations, ~~are entitled to take~~ socio-economic considerations ~~into account~~ in reaching a decision on imports of LMOs, including the value of biological diversity to IPLCs."
126	11-12	We suggest the text edits in red below to reflect that, although no international mechanism is currently in place, there is not an explicit need for one either "In this sense, what is immediately apparent from the international-level mapping described in Sections 8 and 9 is that no specific governance or process of rule-making on an international scale exists to 'regulate' synthetic biology, although the need for such a global mechanism has yet been determined."
126	17-20	We suggested the text edits in red below. We consider that the rationale behind this statement is unclear. We note that the adoption of the term "synthetic biology", which is not defined, after the establishment of regulatory process does not necessitate that those processes require updating. Our suggested edits reflect that new tools have come into use and that there are new *products/applications* that may require updated regulatory mechanisms to assess. "In a similar manner, it is also important to consider that manyost regulatory mechanisms discussed in the present document were developed before some tools that enablethe term synthetic biology became widely used and therefore, they were not developed with the necessary scope and scale that some of the potential impacts of some applications of synthetic biology may present."
129	2-4	We recommend including a reference to support this statement. "Social, economic, and cultural considerations are as equally important as the consideration of potential 2 impacts on biodiversity, conservation and sustainable use during decision-making and governance of 3 synthetic biology applications."
131	27-29	We recommend providing more information as to why biosafety and biosecurity are complimentary approaches in this context. "Foremost, while the objectives are clearly different, it is evident that biosafety and biosecurity, at least in a containment context, are complimentary disciplines that benefit from an aligned approach."
131	36-38	We recommend providing a reference for the statement below. "The rapid advancement of the underlying science and the exponential rise in potential applications of synthetic biology is far exceeding the speed at which national and international governance frameworks can adapt."
132	7-9	We recommend providing more detail and a stronger rationale for the statement below. It is not clear why and how engineered gene drive-modified organisms are an effective lens for viewing all synbio applications.

		"As synthetic biology applications approach commercial deployment and potential environmental release, engineered gene drives provide a useful lens through which to evaluate overlaps and potential gaps in the governance of synthetic biology."
132	30-31	We recommend providing more information, especially for the opposing view. We consider that the following paragraph should not be predicated solely upon a single view. "There is a view that humans should not intervene in nature at all using a technology such as gene drive-modified organisms."
132	43-44	We suggest the text edits in red below to remove the hyperbole and to place this in the appropriate context. "Since the publication of the previous technical series on synthetic biology in 2015, the number of synthetic biology applications has continued to greatly increase~~advance exponentially~~."
132	48-49	We recommend providing more detail regarding what clarity is being achieved. "As the field continues to advance and more applications become available, there is a growing pressure towards achieving clarity."
133	8-10	We recommend providing more information or deleting the statement below. We note that at present, there are no genome-edited animals or gene-drive modified organisms that are close to being released into the market. "Additional products intended for environmental release are in advanced stages of development, such as genome edited animals and organisms containing engineered gene drives to control vector-borne diseases."
133	16-20	We suggest the text edits in red below as the rationale behind this statement is unclear. We note that the adoption of the term "synthetic biology", which is not defined, after the establishment of regulatory process does not necessitate that those processes require updating. Our suggested edits reflect that new tools have come into use and that there are new *products/applications* that may require updated regulatory mechanisms to assess. "It is also noteworthy to consider that m any~~ost~~ ost regulatory mechanisms (i.e those discussed in the present document) were developed before the some tools that enable~~the term~~ synthetic biology became widely used, and therefore may not have sufficient oversight, in terms of scope and scale, for some of some applications of the potential impacts from synthetic biology.
133	27-28	We recommend providing more information, as well as references, to "perceived need" in the statement below.

		"... there is also a perceived need for the development of additional tools to complement this and other existing methodologies."
133	28-30	We suggest the text edits in red below to reflect that not all applications of synthetic biology may require detection and identification, which could reduce strain. "Further, the inability to potentially detect and identify the applications of synthetic biology can add~~s~~ complexity and may strain the abilities of developing nations whose regulatory frameworks may not be (fully) developed, emphasizing the importance of focusing detection on applications that contain inherent risks."

Please submit your comments to secretariat@cbd.int.