

**TEMPLATE FOR PEER REVIEW COMMENTS
TECHNICAL SERIES ON SYNTHETIC BIOLOGY**

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Comments on the Technical Series on Synthetic Biology		
Page #	Line #	Comment
0	0	<p>General comments on the draft document</p> <p>The GIC notes the review carried out by the authors that captures recent as well and earlier biotechnological applications and developments. We recognise that due to the lack of agreed upon definition of synthetic biology, and the very broad nature of the existing operational definition developed by the Ad Hoc Technical Expert Group on Synthetic Biology (AHTEG) in 2015, it is impossible to clearly draw a line between “synthetic biology” applications, and biotechnological applications more generally. The authors point out that they “<i>recognise that some of the processes or products described in this document may not be considered as synthetic biology approaches and applications by all readers, however the broadest interpretation has been made in order to be as inclusive as possible whilst at the same time not championing this interpretation as being definitive. The authors have also attempted to achieve the same degree of inclusivity when presenting the numerous published perspectives concerning individual synthetic biology applications and the sector as a whole.</i>”[p.15, lines 20 - 25]. The GIC believes that due to the approach taken, the draft is not an account of synthetic biology applications, but rather a presentation of any and all biotechnological developments in recent decades. Some of these “developments” are not recent and occurred well before the first Technical Series document of 2015 but were not included in that document. We therefore question the appropriateness of the title of the document as “synthetic biology”.</p> <p>We do not agree with several of the applications that are included as synthetic biology in this updated document, but in particular emphasise our view that genome editing is not synthetic biology – it is a collection of enabling tools that may be used to achieve a range of outcomes. This document includes genome editing as a whole, including a</p>

		<p>commercial example containing a point mutation. Such genetic modifications are comparable to spontaneous mutations, or that which can be achieved using conventional methods, and cannot be considered within the scope of a “<i>new dimension</i>” per the operational definition, even at its broadest interpretation. We strongly recommend that the authors remove examples of applications of genome editing that result in plant and other products that are comparable to products developed with the application of conventional breeding tools, and have been determined by different regulatory authorities as not meeting the definition for a LMO.</p> <p>Our specific editing suggestions and recommendations presented below are intended to draw the attention of the authors to text that needs clarification with our objective being to reduce exaggerated, speculative or hypothetical statements, correct misleading references, and improve focus on actual developments since the publication of the first Technical Series No 82 in 2015.</p> <p>We note that this document was included as an INF document (CBD/SBSTTA/24/INF/19) in the recently convened formal virtual sessions of SBSTTA-24, despite it being a draft and not having completed peer review. The notification for peer review itself states: “<i>Kindly note that the document is a draft, for comments only, and not for citation or other uses.</i>” We therefore question the appropriateness of including it in the SBSTTA INF materials.</p>
1	6	Replace “ <i>cell</i> ” and “ <i>genome</i> ” with “ <i>cells</i> ” and “ <i>genomes</i> ”.
1	22	Replace “ <i>request that the present edition attempts to address</i> ” with “ <i>the present edition attempts to address this request</i> ”.
6-7	-	<p>ABBREVIATIONS AND ACRONYMS Move IGC up OPCW – missing text Delete 1 after ZFN</p>
8 - 15	0	<p>EXECUTIVE SUMMARY – general comments The executive summary presents a biased account of the content of the report and requires editing to reflect factual information presented in the body of the document. It should better reflect that:</p> <ul style="list-style-type: none"> • there is no agreement on the next steps forward. • synthetic biology is not a single entity/discipline and as such different groups define it in different ways. • the definition of synthetic biology used in support of the continuing work on the topic under the CBD is not endorsed by Parties and is thus “work in progress”. • remove speculative statements about gaps in regulation and use of technologies, as well as their impact • edit text to correctly depict enabling tools and technologies <p>A more balanced view should be presented in the summary and specific edits are suggested in the following rows.</p> <p>We also suggest that rather than merely stating that this document is an update [page 9 line 12], there should be a paragraph providing an overview of the new information this “updated” version of the document provides compared to the 2015 version. We also recommend that an explanation and justification is provided for why this document has focussed on genome editing applications, especially such that are not considered LMOs, or such that are clearly captured and handled within the scope of</p>

		existing LMO provisions. The extensive focus on such applications reduces the value of the document that is expected to provide updated technical information of applications of synthetic biology.
8	10	Delete “ <i>genetic engineering</i> ” at the end of first sentence and add text: “... <i>the relatively long-established field of genetic engineering - the foundation of synthetic biology.</i> ”
8	10-12	Delete “ <i>The emergence of several sophisticated technologies has greatly impacted the sector in the last years. As a consequence, the number of applications, especially those that make use of genome editing technology, has increased exponentially and has led to</i> ” and replace with “ <i>The more recent emergence of increasingly sophisticated technologies and tools has greatly expanded the potential range of applications, and facilitated....</i> ” The text is exaggerated and focused on genome editing
8	13-15	It is highlighted that “ <i>Particularly, CRISPR-Cas technology is “having impacts”...</i> ” We do not agree with singling out one type of enabling technology, which is not yet widely demonstrated or “having impacts” despite being an active R&D area. We also question the emphasis on potential agricultural applications. We suggest that the text should be made clearer that: i. this is an enabling technology and not all applications will be “synthetic biology”. ii. what is presented here are <i>potential</i> beneficial applications of certain tools.
8	16	A “ <i>wide variety of organisms</i> ” is also not demonstrated. The text needs to be toned down and factual. The proofs of concept for engineered gene drives remain limited to a small number of insects.
8	17	Insert “ <i>potential</i> ” prior to “ <i>synthetic biology</i> ”.
8	19	Delete “ <i>several</i> ”.
8	21	Delete beginning of the sentence “ <i>although synthetic biology is often referred to as a single discipline</i> ” as it is not considered to be a single discipline but rather it is generally recognized as a combination, as stated above in line 3.
8	22	Replace “ <i>represent a wide array of potential impacts</i> ” with “ <i>... have the potential to result in organisms and products with a range of potential impacts of relevance to the CBD.</i> ”
8	22	Replace “ <i>are</i> ” with “ <i>may be</i> ”.
8	25	Insert “ <i>there are views that</i> ” after “ <i>Therefore,</i> ”.
8	26	Replace “ <i>is seen as</i> ” with “ <i>should be</i> ”. Delete “ <i>one</i> ”.
8	27	Replace “ <i>evaluates such</i> ” with “ <i>incorporates broader considerations such as..</i> ”.
8	27-28	Delete “ <i>alongside a scientific analysis of the expected or potential changes that would result from using technology.</i> ”.
8	28	Delete “ <i>also</i> ”.
8	28-29	Delete “ <i>due to the diverse nature of the</i> ”.
8	29	Delete “ <i>they</i> ”.
8	31	Delete “ <i>commercial deployment and</i> ”. It should be noted that many applications will be deployed in a not-for-profit way.
8	32	Replace “ <i>same</i> ” with “ <i>existing biotech regulatory</i> ”.
8	32-33	Delete “ <i>classical genetic engineering albeit</i> ”.

		<p>The authors use the term “classical genetic engineering” which is not defined and has the potential to be understood differently by different readers. We recommend that the authors do not use this term anywhere in the text of the report, especially when they refer to applications of modern biotechnology that result in LMOs.</p> <p>This term can also misleadingly imply that the existing regulatory and governance mechanisms apply only to such “classical” applications, however these remain applicable for all applications of genetic engineering.</p>
8	33	Insert " <i>or without</i> " after " <i>with</i> "
8	33	Delete " <i>a</i> " before " <i>national</i> "
8	40	<p>Replace "<i>fragmented</i>" with "<i>complex</i>".</p> <p>The review made by the authors does not lead to a conclusion that there is a “fragmented landscape” and the statement is more speculative than factual.</p>
8	41	<p>Replace "<i>creates a complex scenario with the potential for regulatory gaps and areas of convergence to develop.</i>" with "<i>...has aroused the concerns of some that there could be gaps in regulatory oversight. Yet, it is also recognized that there may be areas of convergence that call for greater coordination and collaboration between international organisations on issues of overlapping concern.</i>"</p> <p>This is edited to reflect that “gaps” are not a widely held concern. This is evident in more than a decade of CBD work programs on synthetic biology involving extensive discussions on this exact topic.</p>
9	3-11	<p>Delete the entire paragraph, it is repetitive of previous content and unnecessary. Further, the first sentence (lines 3-6) contains generalisations and is misleading. The author’s conclusion is not substantiated by the review presented in this document. Rather, their review points to the fact that today views remain split on what synthetic biology is and what "novel" elements require new or expanded governance. Furthermore, the last sentence (lines 8-11) implies that R&D is not conducted responsibly today. What evidence can be provided by the authors to substantiate this claim?</p>
9	12	Insert " <i>hereinafter referred to as [insert name of this document]</i> "
9	27	<p>The authors imply that there are products of synthetic biology that are not regulated (“... <i>whether and how...</i>”).</p> <p>We underline and remind the authors that while not all products may be captured for regulation under biotechnology or LMO provisions, they are nevertheless regulated by appropriate product and application specific regulatory provisions (e.g. chemicals, biologicals, etc.). We recommend that this point is considered throughout the text where claims are made that products/processes may not be regulated. It should not be implied that if something is not addressed directly by the CBD then it is not addressed at all, or it is addressed insufficiently elsewhere.</p>
9	28	Replace " <i>used with classical genetic engineering) albeit</i> " with " <i>currently used for biotechnology</i> ".
9	28	Insert " <i>or without</i> " after " <i>with</i> ".
9	29-30	Replace " <i>classical genetic engineering</i> " with " <i>genetic engineering in the 1970s</i> "
9	34-35	Revise. Speculative statements and exaggerations such as " <i>have an impact in an unprecedented manner</i> " , " <i>...the potential of synthetic biology toolbox is boundless...</i> " should be toned down.
9	36-37	Revise. Some of the examples included in the list (Table 1) are not examples of synthetic biology but biotechnology. This needs to be underlined by the authors again in this part of the key messages.

9	46	Replace “ <i>development</i> ” with “ <i>investigation</i> ”.
9	48-49	Delete “ <i>These are only some of the many examples of synthetic biology applications that are having and could have an impact in an unprecedented manner</i> ”. If the sentence is to be retained, the authors must substantiate their claim for “ <i>unprecedented manner</i> ” and provide examples of what exactly is “ <i>unprecedented</i> ” for such applications.
10	6	Revise. Products “ <i>produced in containment e.g. synthetic DNA, synthetic RNA, and oligonucleotides across various industries</i> are not “ <i>new</i> ” or “ <i>synthetic biology</i> ”.
10	10-21	Replace “ <i>supporting</i> ” with “ <i>enabling</i> ” technologies.
10	30-31	Revise. It would be informative to note how many of these global sponsors are public funding bodies.
10	44-45	Revise. The genome editing crops and self-limiting insects are not examples of synthetic biology. Why are such examples now assigned as synthetic biology?
10	47	Replace “ <i>reach the market</i> ” with “ <i>be deployed</i> ” . The gene drive applications currently being developed will not be marketed.
11	11-26	Revise to make more factual. This section does not contain examples of experience so the title should be amended to reflect this. This paragraph is also biased. Its perspective/assumption is that traditional or smallholder cultivation practices are sustainable/ethical and moral/free of human rights and environmental abuses. This is a significant simplification that overlooks real life “nuances”.
11	14-15	Revise for factualness. There is a suggestion that products of synthetic biology “ <i>could also disrupt in situ conservation projects</i> ” – please provide evidence for the demonstration of this.
11	30	Revise for factualness. Why are LCs most likely to be impacted first? This is another example of the authors making biased and broad assumption.
11	32	Replace “ <i>construction</i> ” with “ <i>development</i> ”.
11	35-36	Revise for factualness. The text “ <i>improve public trust through the development of safety measures and policies</i> ” misleadingly implies that this is not the case already.
12	12-15	Delete the two sentences “ <i>The “DIY Bio” community in particular has raised concerns ... low tech laboratory settings</i> ” These are problematic because they incorrectly suggest that the DIY community itself has raised these concerns, rather than the DIY community being the subject of these concerns. But more importantly, the relevance of these two sentences is not clear given that these concerns have been allayed by evidence of their actual activities, capabilities, and proactive approach to biosafety and biosecurity, which are discussed in this document.
12	22	Add the sentence at the end of the paragraph “ <i>Self-regulation through e.g. biosafety and biosecurity education or interviewing (new) participants is also very prominently practiced in the “DIY Bio” community and iGEM initiatives, thereby responding to the concerns raised regarding lack of oversight or containment in these low tech (community) laboratory settings.</i> ”
12	23	Delete “ <i>of those countries form the basis of discussions aimed at reaching a consensus at the international level</i> ”.
12	32	Delete “ <i>this century</i> ”.
12	34-38	Revise for factualness. The paragraph provides assumptions without considering real life “nuances”. Decision making processes under biotech regulatory systems take into

		consideration whatever issues are appropriate according to national circumstances and priorities. A conclusion of there being a need for a "new paradigm" can hardly be justified - more than a decade of discussion on the topic under the CBD has not come to this conclusion.
12	40-45	Revise for factualness. Another real-life nuance here is that developers typically engage regulators early. The gene drive scientific community provide an example of this.
12	42	Revise for factualness. What is the " <i>fast pace</i> " referring to? The CBD discussions have been talking about a "fast pace" for more than a decade and still there are few commercial products outside of contained uses, and the products cited are not "synthetic biology".
12	49	Delete " <i>new</i> " Synthetic biology is referred to as new discipline. Not only is this inconsistent with the broad definition the authors have applied, it fails to recognise that it builds on long-existing disciplines and is part of a continuum of biotechnological developments.
12	50	Replace text. These are broad statements that need to be justified with evidence. It would be more balanced and factual to replace line 50 and state that " <i>...and it is possible that existing regulatory mechanisms may need adaptation on a case-by-case basis to comprehensively assess new types of environmental applications, for example the information required for a risk assessment of an LMO containing an engineered gene drive.</i> "
13	4	Insert " <i>LMO</i> " prior to " <i>biosafety</i> " and delete " <i>conventional LMOs</i> ". LMOs are LMOs, "conventional LMO" is meaningless.
13	5	Delete " <i>already include some of these complex elements</i> " and replace with " <i>accommodate the potential expansion of types of LMOs and applications.</i> ".
13	6	Insert " <i>where necessary</i> " after " <i>frameworks</i> ".
13	9-28	Revise Paragraph 15 for factualness. As it is written, it is misleading - the authors are implying that all synthetic biology uses need to be covered under a single regulatory regime. No products have such regulatory coverage, and this cannot be the case for synthetic biology either (and especially where there is no clear definition of it). This needs to focus clearly on the CBD rather than promote expansion of the CBD regulatory scope (and in the absence of understanding on what is "appropriate" regulations).
13	21	We agree with the phrase " <i>without the need to invent/create another series of fora</i> "
13	31	Delete " <i>fragmented</i> ". The landscape is not "fragmented", it is just multi-faceted.
13	33-34	Revise for factualness. The authors should refrain from using statements such as the following: " <i>there is a growing urgency to discuss the evolution of a more cohesive international regulatory environment</i> " in the absence of evidence in the report for such need.
14	-	Revise Table 1 for factualness. We note that the authors have used 'inclusive' approach to identifying applications of synthetic biology, however some of the listed applications are approved LMOs, LMOs under development, or are products that are not covered under biotechnology regulations and cannot be presented as examples of synthetic biology applications. Please remove the following from Table 1: <ul style="list-style-type: none"> • Transient modification of agricultural plants through RNAi spray or nanomaterials

		<ul style="list-style-type: none"> • Genome edited crop plants and farm animals • Engineered gene drive for an agricultural pest • Genetically engineered sorghum to produce a new synthetic protein to improve the digestibility in food and feed. • Genetically engineered oilseed rape to enhance resource use efficiency of existing cropland • Genome edited soyabean and oilseed rape • Self-limiting insects <p>Please substantiate with evidence that the “<i>engineered drive for an agricultural pest</i>” is in advanced development.</p>
15	11	The statement “ <i>While there is no internationally agreed definition of “synthetic biology”</i> ” should be captured in the Executive Summary which currently misses this nuanced but important information.
15	13	Delete “ <i>is</i> ” and replace with “ <i>they proposed, of:</i> ”
15	19	Insert “ <i>tools,</i> ” prior to “ <i>techniques</i> ” and insert “ <i>and applications</i> ” after “ <i>techniques</i> ”.
15	22	If the broadest interpretation is maintained, the authors are not describing synthetic biology but "modern biotechnology" and "biotechnology" more generally. If the authors do not reduce the scope of applications captured in their report, there should be a consideration whether the report is providing an update on synthetic biology or biotechnology.
17	9	Insert “ <i>body of research identifying itself as</i> ” prior to “ <i>synthetic</i> ” and delete “ <i>research</i> ” from this sentence.
17	15-16	In this sentence it is not clear here how many funding bodies for Germany, Japan, UK, EU
17	18	Replace “ <i>raising</i> ” with “ <i>increasing</i> ”.
17	22	Replace “ <i>could</i> ” with “ <i>are</i> ”.
17	23-24	Delete “ <i>some of the more widely used tools</i> ” and replace with “ <i>biotechnology technologies and tools that have emerged since the 1990s ,</i> ” This is a more accurate description of the following sections, which in essence present information about developments in biotechnology that are not "classic" rDNA approaches, and labels them as synthetic biology.
17	29-30	Delete “ <i>Using proprietary techniques, machines can also create DNA strands up to the size of a gene, hundreds, or thousands of base pairs in length.</i> ” The sentence correctness is questionable and should be deleted unless clearly supported by evidence that “ <i>thousands of base pairs</i> ” can be synthesized (rather than assembled).
17	32	Revise for factualness. “ <i>genome-length DNA strands</i> ” is misleading given that genomes are of different sizes, and the cited article does not provide such examples.
18	5	Revise for factualness. Why is it stated that directed evolution is a “ <i>biotechnology method often employed for synthetic biology</i> ” ?
18	4-25	Major revision needed. The section on genome editing is technically detailed and it lacks context. It is very unclear why this section is not focusing on how genome editing is used in synthetic biology . Why are the outcomes described (e.g. SDN-1 types changes) considered relevant to synthetic biology? Some of these changes might

		be one or very few base pairs, how is this a " <i>new dimension of modern biotechnology</i> "? Even SDN-3, which results in outcomes comparable to so-called "classical" transgenics, cannot be described as a "new dimension".
18	5	Insert " <i>some of which are</i> " before " <i>based</i> ".
18	25	Replace " <i>mammal</i> " with " <i>mammalian</i> ".
18	32	Delete " <i>supposed to be</i> " and replace with " <i>subsequently</i> ".
19	4	Replace " <i>having impacts in agriculture, especially in</i> " with " <i>being applied with the aims of</i> " This will ensure the language is neutral and factual.
19	6	Combining agricultural traits is also possible with conventional breeding techniques, it is just more efficient with genome editing.
19	18	Targeted point mutations are not synthetic biology. Point mutations are possible with other techniques that are not biotech. This is not a "new dimension".
19	27-28	Revise for factualness. The cited article does not provide for such description of gene drive. The authors should review and update this text to avoid using "selfish" "Mendel's laws of independent assortment" , "favour their own inheritance" - all of which lack scientific rigour. Consider using the publication: Standardizing the definition of gene drive Luke S. Alphey, Andrea Crisanti, Filippo Randazzo, Omar S. Akbari (2020) PNAS , 117 (49) 30864-30867; DOI: 10.1073/pnas.2020417117
19	32-34	The sentence captured here also applies to "genome editing". The genome editing section should be written in a similar way to this section - instead of just describing techniques it should describe applications that are/may be relevant to synthetic biology.
19	38	It should be noted that frequency of gene inheritance can be the result of other mechanisms such as natural selection
19	41	Delete " <i>can</i> " and replace with " <i>may</i> ".
19	41	Insert " <i>Laboratory-based testing indicates that</i> " before " <i>These CRISPR</i> ".
20	7	Delete " <i>rapidly</i> ". How "rapidly" it spreads depends on the generation time of the species. Take care to be factual and not imply spread at an uncontrollable rate.
21	7	Remove the additional " <i>t</i> " from " <i>titter</i> ".
22	27-30	Missing reference A reference is needed to support this sentence.
23 -29	0	Revision needed. The " <i>Areas of Synthetic Biology research</i> " section is a highly confused review of developments in biotechnology and genetic engineering. At times the authors define synthetic biology as a field and at other times as tools that are used for achieving different engineering goals. It is not clear how this patchwork of information helps the reader to understand what the areas of are research where concepts of synthetic biology are actively pursued. This section contains what is "considered" by the authors to be synthetic biology. This needs to me more factual, e.g. areas of research that have emerged that have been referred to as synthetic biology under the CBD (or by practitioners), but there is no general consensus on this list. It is demonstrated (particularly in the following section 3) that these are not brand-new areas of research but are the current state of the art in a continuum of development from discoveries made decades ago.

23	20	Delete “ <i>synthetic biology</i> ”.
23	25	Missing reference “ <i>Monod’s Nobel prize-winning work</i> ” was in 1965! Add reference to the year to underline the time frame.
23	29	Missing reference Please specify from when “ <i>Another 40 years passed...</i> ”
23	34	Revise Describe what were the two discrete states of switch described in “ <i>was a toggle switch in E. coli</i> ”, otherwise this is of little value as information.
23	Footnote 7	“ <i>not frequently included when synthetic biology is discussed,</i> ” What does this mean? Not discussed under the CBD? There needs to be better explanation in the introductory paragraph lines 16-18 regarding what is included/excluded in this section with reasons.
24	38-39	Delete “ <i>are working</i> ” and replace with “ <i>have long worked</i> ” This is not new at all - commercial GM crops have optimised Bt protein expression.
25	10-12	Revise for factualness. The introductory sentence does not make sense, and it is not true. This can be stated more factually and clearly, e.g. “ <i>Metabolic engineering aims to optimise biological production of biochemicals.</i> ”
25	14	Revise for factualness. The use of the phrase “ <i>with classic genetic engineering techniques.</i> ” suggests that the tools of genetic engineering remain static while synthetic biology advances and uses a substantially different set of tools which is not the case. Synthetic biology is based on “classic” genetic engineering, it is just an extension of it. In reality, synthetic biology (as broadly described by the authors in this tech review) is the state of the art of genetic engineering and biotechnology of today.
25	14	Revise for factualness. What is “ <i>first wave</i> ”? This sentence describes “classic” genome editing for a specific application, not “first-wave” synthetic biology.
27	30	Revise for factualness. The statement that “ <i>xenobiology is the study of unusual life forms</i> ” needs to be edited.
28	25	Replace “ <i>cocktail of chemicals</i> ” with “ <i>conditions to survive</i> ”
29	12-15	Revise for factualness. A more factual representation of these sentences would be: “ <i>The advances in biotechnological tools and techniques since the late 20th century have provided a diverse toolbox for practitioners for a range of potential applications and products. This section describes specific examples and is not an exhaustive list.</i> ” Synthetic biology does not provide an “ <i>unprecedented toolbox</i> ” and it should be noted that the many of the examples given subsequently should not be classified as synthetic biology.
30	2	We agree with the authors in their labelling of bacteria as genetically engineered, which underlines the point that not all examples provided in the text can, or should be classified as synthetic biology.
30	27	“ <i>Synthetic biology applications</i> ” is used misleadingly as an umbrella term of any development in biotechnology.
30	28-29	Delete “ <i>island communities</i> ” and replace with “ <i>indigenous species on islands</i> ”.
30	30	Delete “ <i>use</i> ” and replace with “ <i>potential application</i> ”.
30	42	Delete “ <i>Synthetic biology is currently being applied to conservation (Piaggio et al., 2017). In ocean ecosystems...</i> ” and replace with , “ <i>The potential for synthetic biology in conservation applications is currently being investigated, for example in ocean ecosystems.</i> ”

31	3	Delete “ <i>Terrestrial organisms are also being subjected to research.</i> ” And replace with “ <i>Applications for terrestrial organisms are also being examined.</i> ”
31	14-32	Revise for factualness. The examples provided in Section 3.2.1 should be removed as none of these can be claimed to be examples of synthetic biology. For example, in lines 24-26 a product is referred to that contains a point mutation which is clearly not synthetic biology. The outcome is a trait that already exists as it can arise via mutation using conventional (non-biotech) tools.
31	33	Revise for factualness. None of the examples described in Section 3.2.2 (a) can be claimed to be synthetic biology. They are examples of products that are similar to conventional ones. “ <i>Advanced Development</i> ” is not true for all of the examples that follow. It would be more correct to say “In development” for some, and others belong in the “research” section. “Advanced” implies it is not far from “commercially available” (the category above). None of the gene drive examples are “advanced”, even the most developed applications are years from field testing. The agricultural example was a proof of concept (research).
32	7	Insert “ <i>one that confers</i> ” after “ <i>modifications</i> ”.
32	7	Insert “ <i>another that confers</i> ” before “ <i>The ability</i> ”.
32	8	Delete “ <i>wild</i> ”.
32	8	Revise for factualness. “ <i>advanced stage</i> ” suggests that unrestricted releases are imminent - this is not the case. It would be more accurate to state that research has thus far been conducted in containment and may advance to field-releases in the foreseeable future.
32	11	Revise for factualness. The use of “ <i>but</i> ” is incorrect since the previous example is also in contained conditions.
32	18	Replace “ <i>wild population</i> ” with “ <i>wild-type</i> ”.
32	20	Revise for completeness. This section should reference more recent Oxitec technology. The self-limiting technology still constitutes a bio-contained system because the transgenic insects do not survive after a few generations.
34	8	Revise for factualness. “ <i>Transient modification of agricultural plants through RNAi spray or nanomaterials</i> ” – this is not an example of synthetic biology. There is no description about what “nanomaterials” the authors refer to or why the authors have identified the application of RNA as an example of synthetic biology. The authors should note that another regulatory forum, under the OECD is addressing the regulation of such future products.
34	27-28	Revise for completeness. Why is “ <i>Genetically engineered plants to produce recombinant polyclonal antibodies against snake venom toxins.</i> ” a standalone category?
40	7-9	Revise for factualness. Lines 7-9 suggest that the number of commercially available and advanced stage synthetic biology applications has greatly increased. This statement must be supported by evidence. We recommend that the authors provide a table that compares information in the Technical Series document from 2015 and this new edition.
40	25-26	Revise for factualness or delete . None of the examples given are products of synthetic biology.

40	28	Revise for factualness. “ <i>engineered gene drives to control vector-borne diseases</i> ” are not advanced! They have progressed from "early stage" but cannot be "advanced" if they have not been tested outside of strict containment.
41	8	Replace “ <i>which are equally</i> ” to “ <i>which may be</i> ”. They are not "equal" - this is a generalisation. They vary in importance according to the priorities and circumstances of the jurisdiction.
41	13	Delete “ <i>Although synthetic biology is often referred to as a coherent and single discipline,</i> ” or define where it is referred to in this way. The "operational definition" used in this document is not consistent with this statement.
41	15-16	Replace: “ <i>In trying to describe such impacts, a multitude of factors need to be discerned.</i> ” with “ <i>Products developed using synthetic biology approaches, as with any product, may have potential impacts on the conservation and sustainable use of biological diversity and it is important to perform a risk assessment prior to their introduction to identify, and if necessary manage the risks which may occur. Similarly, the socio-economic impacts of a product of synthetic biology may be assessed as in any other case.</i> ”
41	45	Delete “ <i>have yet been commercialised</i> ” and replace with “ <i>are near deployment</i> ” The term "commercialisation" does not apply to all of the potential applications, as most will be for public good rather than "commercial" purposes.
42	20-23	Sentence refers to off-target mutations with genome editing. To present context and be more complete, it should also mention recent scientific reviews. For example, EFSA concluded that off target mutations are likely to be fewer in edited organisms that in conventionally bred organisms. EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), Naegeli H, Bresson J-L, Dalmay T, Dewhurst IC, Epstein MM, Firbank LG, Guerche P, Hejatko J, Moreno FJ, Mullins E, Nogue F, Sanchez Serrano JJ, Savoini G, Veromann E, Veronesi F, Casacuberta J, Gennaro A, Paraskevopoulos K, Raffaello T and Rostoks N, 2020. Applicability of the EFSA Opinion on site-directed nucleases type 3 for the safety assessment of plants developed using site-directed nucleases type 1 and 2 and oligonucleotide-directed mutagenesis. EFSA Journal 2020;18(11):6299, 14 pp. https://doi.org/10.2903/j.efsa.2020.6299
42	19	Delete “ <i>is native or</i> ” as this section is discussing IAS.
42	37	Replace “ <i>The most advanced application</i> ” with “ <i>the most advanced type of use of the technology</i> ” is for malaria vector control”.
42	45	Replace “ <i>sibling</i> ” with “ <i>related</i> ”
43	2-3	This is a generalisation that is inconsistent with the Collins paper referenced above (page 42 line 48) – this states that there is one predatory species with a specialisation on blood-fed mosquitoes including <i>A. gambiae</i> – <i>Evarcha culicivora</i> s. This jumping spider, known as the vampire spider, is found around Lake Victoria. There is no evidence that these salticids require <i>Anopheles</i> mosquitoes and will readily consume blood-fed <i>Culex</i> .
43	22	Is this referring to replacing or providing an additional trait (as suggested in line 18)? Suggest revising: Replace “ <i>replace a population</i> ” with “ <i>replace a specific trait within a population</i> ”
43	24	Insert “ <i>sexually compatible</i> ” before “ <i>species</i> ”
43	27	Regarding the term “ <i>synthetic biology organism containing an engineered gene drive</i> ” - even within the CBD, this category of organisms is termed “living modified

		organisms containing engineered gene drives”. Recommend that the authors should maintain this terminology.
43	29	Delete “ <i>synthetic</i> ”
43	43-45	Research to overcome resistance should also be mentioned.
43	47-48	The term "ecosystem services" and the examples provided relate to humans, not to non-target organisms.
43 44	46-49 1-10	This paragraph needs better placing into context. The concept of controlling/removing or introducing new/different species is not new or unique to synthetic biology. There are precedents for comparison, e.g. other LMOs and other disease vector/pest control strategies. In discussing the potential risks, they should not be considered in isolation (which exaggerates them) but in comparison to other tools that are used for addressing the problem. It should also be noted that where there are potential significant public health benefits, morally and ethically this could necessitate consideration (and weighing) of both the potential benefits and risks. It is odd that this document stresses a range of factors as important in decision making elsewhere (e.g. p18, lines 8-9; section 5) but this section is narrowly confined to environmental risks.
44	3	Please note that lower numbers are not the expected result of replacement drives.
44	16-18	Revise for factualness. The cited authors are not gene drive developers.
44	17	Insert “ <i>certain</i> ” before “ <i>gene drive</i> ”. The likelihood of invasiveness is a consequence of the design of the drive. Therefore, this statement cannot be made in general for gene drives as a whole.
44	20-24	This sentence presents (another) generalisation of risk and has a questionable rationale. Elsewhere in the report the authors highlight case-by-case assessment. As for other LMOs, the risks would be assessed prior to introduction with risk management measures introduced as necessary.
44	25	Revise for factualness. Multiple examples used by the authors in section 4.2 are not related to synthetic biology and should be deleted. Just because a developer is using Crispr/cas, or any other current biotechnology tools does not make the product a synthetic biology product.
44	30-31	Delete “ <i>and that provide alternative weed control (e.g. Cibus’ oilseed rape resistant to CLEARFIELD® herbicides)</i> ” or provide a reference to back the claim that this is an application of synthetic biology.
44 45	41-48 1-19	Genome edited plants are not the outcome of applications of synthetic biology and therefore the examples listed are not relevant and should be deleted (page 44, lines 47-48; page 45, lines 1-4). Further, on the topic of off-target mutations, as we have already pointed out, the European Food Safety Authority (EFSA) concluded that off-target mutations are likely to be fewer in edited organisms than in conventionally bred organisms. They also concluded that genome editing techniques that modify the DNA of plants do not pose higher of different hazards than conventional breeding or techniques that introduce new DNA into a plant. Revise for completeness: We suggest reviewing and referring to a broader sample of the scientific literature on this topic in the paragraph on page 44, lines 41-46. Delete entirely the paragraph on page 45, lines 5-19, it is not relevant to synthetic biology.
45	20-21	Revise for factualness. “ <i>Concerns have also been raised surrounding the generation of plant allergens, toxins and anti-nutrients, which may pose a risk to human and animal health</i> ”

		Please provide context to this statement, and indicate that this is a standard consideration in the case by case risk assessment of LMOs.
45	27 (and elsewhere)	The authors must clearly identify the scientific merit of the publications they refer to. It is highly misleading to compare genuine scientific information that provided by interest group materials. If used, these need to be acknowledged.
47	25	Missing reference. “ <i>disrupt in situ conservation projects</i> ” Please back this statement with a research article demonstrating such potential.
47	37 -38	Please add a note on the difference between vanilla (the natural product) and vanillin (the synthesised compound). Vanillin and vanilla compete in different markets (see e.g. https://www.nature.com/articles/nbt.3191).
47	36	Delete “ <i>seems to</i> ” and add “s” to “ <i>support</i> ”
47	40	Insert “ <i>compared to the vanillin molecule</i> ” after “ <i>profile</i> ”
47	40	Replace “ <i>As a consequence, UNCTAD expect that the naturally sourced product</i> ” with, “ <i>According to the report, naturally sourced vanilla.</i> ”
48	1	Insert “ <i>voluntary</i> ” before “ <i>guidance</i> ”. Insert “ <i>in the context of reaching a decision on LMO import per Article 26 of the Cartagena Protocol</i> ” after “ <i>concerns</i> ”. Replace “ <i>has recently emerged</i> ” with “ <i>is in development and yet to be considered or adopted by CP Parties</i> ”
48	8-27	Revise for factualness. The whole first paragraph in section 5.1.1 is highly biased. Some specific edits are suggested below, however further revision by the authors is recommended.
48	8	Replace “ <i>concerns</i> ” with “ <i>considerations</i> ”
48	13	Insert “ <i>science based</i> ” before “ <i>risk assessment</i> ” Insert “ <i>conducted in accordance with the principles set out in the Cartagena Protocol.</i> ” after “ <i>risk assessment</i> ”
48	17	Replace “ <i>must be included in the process of judging</i> ” with “ <i>influence judgement of</i> ” Regarding the sentences in lines 14-18 – this process is not new or specific to synthetic biology, and does not need to be “fixed” to accommodate synthetic biology. It should always be the case that decisions are determined by a robust assessment of the potential risks of the product, with that assessment and decision-making process shaped by policy aims that take into consideration the needs of society. These processes are determined at the national government level according to national priorities and circumstances. It is not the scope of this document (or CBD) to instruct on policy making.
48	18-20	Revise for factualness. What types of applications are being referred to here? Is this mixing medical applications (not in scope) with those intended for environmental release? For the agricultural examples presented in this document, there are ongoing discussions about the appropriate level of regulation within existing biotech frameworks, not about “responsible application”.
48	21	Revise for factualness. “ <i>which are likely to be the first to feel any potential impact</i> ” What evidence can be provided to support the claim? If the statement reflects views of specific organisations, this should be acknowledged as an opinion, not a fact.

48	22	Replace “ <i>Thus, the acceptability of any risk is a social construct, as are the</i> ” with “ <i>The level of risk that is acceptable in a society will depend on many factors...</i> ”
48	23	Revise “... <i>should be informed through consultation with a broad set of stakeholders</i> ”. This seems to be prescribing how national governments should develop policy? We note again, that national decision-making is not the scope of this document or the CBD.
48	28	Missing reference. “ <i>technologies that affect the global commons</i> ”. What technologies are you having in mind here? Also, please add an explanation of what “global commons” is to make it easier for the reader to understand what is discussed in this paragraph.
48	29	Revise for factualness. “... <i>should be published in advance</i> ”. This is what happens - normal scientific practice is to publish research concepts, and results of early stage research.
48	31	Revise for factualness. “... <i>conventions</i> ” is this referring to adaptation of Treaties?
48	38	How are “new breeding techniques” as a whole relevant to synthetic biology?
51	1	Replace “ <i>concerns</i> ” with “ <i>considerations</i> ”
51	6	Replace “ <i>import and export</i> ” with “ <i>transboundary movement</i> ”
51	26	Replace “ <i>for wild caught species</i> ” with “ <i>for products from wild species</i> ”
51	27-29	Please add examples to the sentence “ <i>Further... synthetic chemistry</i> ”
51	35	Delete “ <i>rather than artificial</i> ” The contrast between “natural” and “artificial” is misleading (and itself artificial)
51	36	Replace “ <i>displacement</i> ” with “ <i>substitution</i> ”
51	37	Delete “ <i>negative</i> ”
51	48	Replace “ <i>using synthetic biology techniques via fermentation in yeast</i> ” with “ <i>by yeast fermentation</i> ”
52	2	Replace “ <i>synthetic biology vanillin</i> ” with “ <i>vanillin from yeast fermentation</i> ”
52	4-7	Please indicate what “potential adverse effects” could arise.
52	35	Replace “ <i>concerns</i> ” with “ <i>considerations</i> ”
53	15	Revise for factualness. “... <i>concentrate power with a few corporations</i> ”. Statements such as this should be supported by evidence instead of by references to work by interest groups or NGO claims. Fact: CRISPR patents are not owned by corporations.
53	33	Revise for factualness. “... <i>novel mode of action</i> ”. What is this referring to? Genetic engineering is not “novel”.
54	6	Insert “ <i>the human values of</i> ” before “ <i>self-determination</i> ”
54	26	Replace “ <i>concerns arising from dual use</i> ” to “ <i>Considerations related to dual use organisms</i> ”
54	27	Please provide a definition of “dual-use” at the beginning of this paragraph.
55	26	Revise for factualness. The statement “ <i>no country regulates the sales of synthetic DNA</i> ” is factually incorrect. Countries may not regulate DNA synthesis and sales under GMO regulations, however a number of health and safety regulation apply, as well as product safety and product quality regulations that also have provisions for consumer / user protection. Environmental liability regulations / legislation equally are fully applicable.

56	36-44	The section is supposed to address “ <i>general biosafety concerns related to the accidental or intentional release of organisms resulting from synthetic biology</i> ”, and it further intends to address “ <i>the suitability of existing risk assessment methodologies as well as potential management strategies</i> ”. Yet, the three specific examples that have been selected (engineered gene drives, gene editing and RNAi sprays) add little value in clarifying what are these specific challenges. Specific comments addressing problematic elements in the text in this chapter are provided in the comments below.
56	36	Replace “ <i>concerns</i> ” with “ <i>considerations</i> ”
56	38	Replace “ <i>concerns</i> ” with “ <i>considerations</i> ”
56	47	Replace “ <i>less</i> ” with “ <i>no, or little</i> ”
57	2	Replace “ <i>products</i> ” with “ <i>organisms</i> ”
57	6	The reference is of questionable relevance – sources with regulatory expertise should be used.
57	10	Replace “ <i>This process will be influenced</i> ” with “ <i>While the risk assessment should be based on specific science-based hypotheses, the final decision will be influenced</i> ”
57	15	Revise for factualness. “... <i>novel risks and impacts, the high levels of uncertainty</i> ”. Has this really happened yet? The regulators participating in the synthetic biology work under the CBD over recent years indicate that it has not.
57	17	Missing reference. Revise for factualness. “ <i>ever-increasing pace of development of these technologies</i> ”. Statements like this need to be supported by evidence - and it is not supported by the information in this document.
57	23-25	Delete last sentence. Repeating content in 5.1.1 - suggest removing it from this section.
57	27-28	Delete “ <i>what could go wrong and</i> ”
57	40	Delete “ <i>the ‘Points to Consider’ in</i> ”
57	40-41	Delete “ <i>of the Protocol</i> ”
57	41-42	Delete “ <i>is a good summary of the types of information that are regularly considered during a risk assessment</i> ” and replace with “ <i>sets out the general principles of a science-based risk assessment, and general methodology including ‘points to consider’</i> ”
57	42-43	Delete “ <i>and that may be extended/adapted to some applications resulting from synthetic biology.</i> ”
57	46	Section 6.1.1 This section needs to mention that there are different types of drives with different potential scales of dispersal.
58	10	Delete “ <i>unprecedented</i> ”
58	10-12	Revise for factualness. The conclusion sentence in line 10-12 contradicts with the summary at the beginning of the paragraph [line 47, page 57 to line 7, page 58]. The authors are recommended to point out that experienced risk assessors (references provided in the beginning of the paragraph) are not identifying the same concerns as these identified by interest groups or civil society campaigners (last reference in the paragraph). Insert at the end of the sentence on line 12 “ <i>However, there are established risk assessment paradigms that could be utilised, such as the regulation of bio-control agents.</i> ” at the end of the sentence.

58	23-29	<p>Revise for factualness. Insert references to support the fact that the general principles and the case by case approach in existing risk assessment methodologies remain applicable for such organisms.</p> <p>It is recommended that the authors place the specific challenges identified in relation to organisms containing engineered gene drive in the context of the general risk assessment methodology as captured in Annex III of the Cartagena Protocols which states that <i>“The process of risk assessment may on the one hand give rise to a need for further information about specific subjects, which may be identified and requested during the assessment process, while on the other hand information on other subjects may not be relevant in some instances”</i>. This will introduce the needed balance to this biased text.</p>
58	33	What is the “complexity of organisms” referring to?
58	37-38	Please add comment that the use of modelling in risk assessment is not novel
58	40	Insert <i>“(depending on the type of drive)”</i> after “areas”
58	45-49	<p>Revise for completeness. The authors present the discussion about regulation of genome editing as part of the discussions on synthetic biology. This is misleading, as we have noted in other parts of this review.</p> <p>If retained, the text should be developed further by adding information on who is holding different views. It will help the readers of the document to understand what are the approaches taken by regulatory bodies and risk assessment bodies, what are the views of scientific bodies, and what are the views of interest and civil society groups.</p>
58	46	Insert <i>“because the changes are equivalent to those that already exist (via conventional breeding or transgenesis) and for which there is a history of safe use”</i> after “negligible risks”
59	12-13	Revise for factualness. The reference to the Court of Justice of the European Union, 2018, is questionable and should be deleted.
59	36	Revise for factualness. Note that “hazard” is not the same as risk.
59	37-39	Please add comment that these “points to consider” are not unique to genome editing but can also apply to transgenesis.
59	46	<i>“... equivalent to changes expected from classical breeding”</i> . Note that the same applies to plants.
60	5-7	Revise for factualness. On line 7 “others” is used. Please review if more than one or just the risk assessor of the EU – EFSA? Several other regulators have not had issue assessing these types of LMOs.
60	11-12	Delete <i>“However, it has also been noted that the risk assessment of RNAi based plants presents some peculiarities compared with that of currently commercialised GM crops.”</i> . Risk assessment has been carried out by multiple regulatory agencies on a number of RNAi-based plant products and some have been commercialised. The authors are recommended to consult regulatory agencies’ sites and product registration information to update their review.
60	18-22	Delete . This is dated information, about dated technology, and too much detail about EFSA. Regulatory approvals were granted prior to the release of the first SB technical series.
60	24-25	<p>Revise for factualness. <i>“...how different regulators perceive novelty”</i></p> <p>The text in this section falsely implies that risk assessment procedures are limited to one type of LMO. In reality, these can be applied to any LMO on a case-by-case basis.</p>

60	27	Insert “ <i>therefore</i> ” after “ <i>systems</i> ”
60	28	Delete “ <i>Thus, it represents a novel</i> ” and replace with “ <i>Such products are a</i> ”
60	29-30	Delete “ <i>it is important that safety assessments for plant protection products are adapted to allow introductions of this technology</i> ” and replace with “ <i>their safety assessment as a plant protection product may be required for their introduction.</i> ”
61 62	45-47 1-20	Delete sections 6.2.1 and 6.2.2 – this is dated information and not new developments.
62	21	Revise for completeness. This section should also include a discussion of strategies to limit spread via split or multi-component drives, which are biocontainment approaches as opposed to the others described in the following section and the next, which are designed to reverse a drive.
64	4	Replace “ <i>Current</i> ” with “ <i>Approved</i> ”
64	8	Delete “ <i>classical genetic engineering</i> ” and replace with “ <i>recombinant DNA approaches</i> ”
64	9	Delete “ <i>synthetic</i> ” Insert “ <i>if subject to GMO regulatory provisions</i> ” after “ <i>organisms</i> ”
64	18	Insert “ <i>technically</i> ” prior to “ <i>feasible</i> ”.
64	31	Insert at the end of the sentence “ <i>although these are isolated cases in seed materials and generalizations based on these cannot be made.</i> ” While the Chhalliyil reference shows that it is possible to detect a DNA change - it is not possible to distinguish whether the DNA change occurred as a result of genome editing or other breeding methods, or occurred spontaneously. For completeness, please add information from the publication: Evaluation of the scientific publication: “A Real-Time Quantitative PCR Method Specific for Detection and Quantification of the First Commercialized Genome-Edited Plant” P. Chhalliyil et al. in: <i>Foods</i> (2020) 9, 1245 by the European Network of GMO Laboratories (ENGL)
64	32-33	Insert at the end of the sentence “ <i>...or an artifact due to the specific reference genome used as the reference</i> ”. Again we question how this can be synthetic biology.
64	33-36	Insert at the end of the sentence “ <i>... or whether this difference is present in the general plant population</i> ”.
64	40	Insert new sentence prior to “ <i>Thus, to...</i> ” “ <i>In recombinant DNA approaches, screening of genetic elements is commonly used to identify materials (Morisset et al 2014). However, each edit will be unique, so that there will be no ‘screening’ strategy available for a range of products. This further increases the challenge of analyzing heterogeneous samples.</i> ” Reference: Morisset D, Novak PK, Zupanič D, Gruden K, Lavrač N, Žel J. GMOseek: a user friendly tool for optimized GMO testing. <i>BMC Bioinformatics</i> . 2014 Aug 1;15(1):258. doi: 10.1186/1471-2105-15-258.
64	43	Replace “ <i>organisms were regulated</i> ” with “ <i>organisms were to be regulated in the country or region where they are grown or imported.</i> ”
64	45	Add at the end of the sentence “ <i>However, the latter view assumes that there will be more sequence changes than typically seen in commercial products and does not consider the breeding and selection process involved in the development of a plant variety.</i> ”

65	0	<p>General comment – we note the authors comment that the “<i>magnitude of recent changes in the field of synthetic biology ... are the main focus of the document</i>” (page 15, lines 28-29). However, half of this (lengthy) document is on the topic of “<i>Synthetic biology governance and regulatory perspectives</i>” (Section E), and this consists of substantial text that is simply copied directly from the 2015 technical series document, or is copied with minor changes and/or additions. This content could be greatly reduced by referring to the 2015 technical series and only providing relevant information that is actually an “update”.</p> <p>For example (not exhaustive), Section 9.3.1 “<i>Risk of harm</i>” (from page 103 line 38 to page 108 line 23 – this is a direct copy from pages 76-80 of the 2015 document). Also, the entire information on “<i>contained use</i>” (page 88 – direct copy of pages 87-88 of the 2015 document); <i>Codex Alimentarius</i> (page 125 – direct copy of page 99 of the 2015 document); and the <i>International Convention for the Protection of New Varieties of Plants</i> (pages 118-120 – direct copy of pages 109-120 of the 2015 document). The sections on the Convention on Biological Diversity (Section 8.1), the Cartagena Protocol (Section 8.2) and the Nagoya Protocol (Section 8.4) are also substantially similar to the 2015 text.</p>
65	7	Add at the end of the sentence “ <i>However, adding such 'signatures' to organisms that have single or few nucleic acid changes is not feasible and defeats the object of making very small changes.</i> ”
65	10	Insert new sentence prior to “ <i>Further...</i> ” “ <i>However, it has not proven possible to differentiate proteins that have for example a single amino acid change, which is what many edits may result in, particularly if that change is in the active site of the protein.</i> ” Replace “ <i>Further is was proposed</i> ” with “ <i>It has been proposed</i> ”
65	16	Insert “ <i>currently</i> ” after “ <i>were</i> ”
65	35	Delete “ <i>will</i> ”
65	35	Insert “ <i>a range of broader considerations, including</i> ” after “ <i>influenced by</i> ”
65	36	Delete “ <i>considerations</i> ” and replace with “ <i>aspects</i> ”
65	39-44	Revise for factualness. We question how true the statement “ <i>as regulatory authorisation is increasingly being sought</i> ” is. Are there references or figures to support this statement? Increased activity is more likely to be developers seeking regulatory clarity from authorities. However, the fact that regulators have been discussing what is the appropriate regulatory approach to genome editing and other technologies, does not imply that such discussions took place under the umbrella of synthetic biology. Perhaps a more accurate statement would be that in addition to consideration on synthetic biology, regulators have been addressing other enabling technologies, including genome editing and others.
65	46	Delete “ <i>wide</i> ”
65	47	Delete “ <i>will</i> ”
65	47	Insert “ <i>LMO</i> ” prior to “ <i>regulatory purview</i> ”.
66	1	Delete “ <i>appeared as</i> ” and replace with “ <i>are recognised as comparable to</i> ”
66	1-2	Delete “ <i>untargeted due to radiation-based or chemical mutagenesis or targeted by the use of transgenesis or genome editing technologies</i> ” and replace with “ <i>.... depend in most cases on whether modifications are comparable to that arising via spontaneous processes or introduced with the use of conventional mutagenesis tools such as</i> ”

		<p><i>irradiation of chemical treatment, or comparable to modifications achieved using transgenic approaches"</i></p> <p>The intended message in this sentence is unclear; edits are suggested for clarity according to our understanding of the regulatory situation.</p>
66	3	Insert " <i>For instance</i> " before " <i>those</i> " in the beginning of the sentence.
66	4	Delete " <i>genes</i> " and replace with " <i>(or exogenous) DNA</i> "
66	5-6	Revise for factualness. " <i>...existence naturally or through conventional breeding</i> ". How can this be an example of "synthetic biology"?
66	8	Delete " <i>most</i> " and replace with " <i>many</i> "
66	9	Delete " <i>Therefore, at one end of the range is</i> " and replace with " <i>The approaches include</i> "
66	11	Insert " <i>on the basis that these do not present novel risks</i> " after " <i>methods</i> "
66	12	Insert " <i>some of</i> " before " <i>those</i> " in the beginning of the sentence. Not all countries that have created exclusions are CP parties (e.g. Australia)
66	34	Insert " <i>Australia</i> " to the list of countries. (legislative changes to exclude SDN-1 from the scope of GMO regulation have been implemented in Australia)
66	37	Delete " <i>e</i> " from " <i>especial</i> "
67	11	Insert " <i>certain</i> " before " <i>genome edited</i> ".
67	12	Revise for factualness. " <i>...products therefore, there is no point in having them regulated</i> " The statement is misleading and misrepresents the discussions on the topic. A more accurate statement would be that because such products are very similar or identical to products developed with conventional tools and methods, the risks are equally comparable and therefore capturing such products under regulation for GMOs may be disproportionate.
67	12-15	Delete " <i>However.....; (Ribarits et al., 2020)</i> " This is repetitive of section 6.2.5 and could be deleted here.
67	21	Delete " <i>from</i> " and replace with " <i>in</i> "
67	22	Insert " <i>potentially</i> " before " <i>has the ability</i> ".
67	32	Insert " <i>adequacy of existing approaches to environmental risk assessment</i> " after " <i>principle</i> ". Insert " <i>participation of the IPLCs that may be affected through the...</i> " before " <i>obtention</i> " Insert " <i>their</i> " before " <i>FPIC</i> "
67	33	Delete " <i>of IPLCs</i> " Check name spelling in provided reference
67	35	Delete " <i>the apparent</i> " and replace with " <i>claimed</i> " Delete " <i>the</i> " before " <i>regulatory</i> "
67	38	Insert " <i>that enables improved knowledge and understanding of the technology</i> " after " <i>laboratory research</i> ".
67	43-46	Revise for completeness and balance. If this NGO statement (" <i>... are currently the best home</i> ") is included here, then others should also be included, e.g. the more strongly supported view that there needs to be collaboration between the CBD and other international fora such as the WHO, which

		has relevant public health expertise and already established procedures that are applicable to mosquitoes containing engineered gene drives.
67	44	Revise for factualness. “ <i>substantive work</i> ” is used to describe the work on gene drives under the CBD. Proposals have been made, but nothing has started yet.
68	1	Insert “ <i>LMO</i> ” before “ <i>regulatory</i> ”.
68	2	Revise for factualness. “ <i>...urgent need...</i> ” This is not consistent with the statement on page 60 line 30-33: “ <i>Existing plant protection product risk assessment approaches can be reliably used to evaluate dsRNA-based products for topical application, with adaptations only required on a case-by-case basis where additional research might be necessary to assess risk (Mezzetti et al., 2020).</i> ”
68	47	Delete “ <i>their</i> ” and replace with “ <i>an enabling</i> ”.
70	41	Revise for factualness. “ <i>concrete agreements</i> ” What about commitments made and principles developed by the gene drive research community? E.g. : - commitments to the safe and responsible development of gene drive technology - Akbari et al 2015 Science doi: 10.1126/science.aac7932 - guiding principles for gene drive research - Emerson et al 2017 Science doi: 10.1126/science.aap9026
72	10	Replace “ <i>form</i> ” with “ <i>from</i> ”
72		Add a new section “ <i>7.3.5 Community Biology Biosafety Handbook</i> ” “ <i>Another example of self-regulation, specifically in the area of “DIY Bio” can be found in the Community Biology Biosafety Handbook, an open manual that offers biosafety protocols, practices, and recommendations aimed specifically at community biology initiatives. Authored by biosafety experts and formed community lab leaders, the manual includes biological, chemical, and equipment safety, as well as specific citizen science topics such as interview practices for screening potential lab members. Given that biotechnology, synthetic biology and community biology are rapidly evolving, the manual was conceived as a living document, to be edited, updated and expanded by the community members.</i> ” Reference: Community Biology Biosafety Handbook (Angela Armendariz, Patrick D’Haeseleer, David Gillum, Daniel Grushkin, Eric Harness, Todd Kuiken, Jenny Molloy, Community Biology Biosafety Handbook, Google Docs ed., Genspace & North Carolina State University, 2020 https://www.genspace.org/community-biology-biosafety-handbook)
72	38	Replace “ <i>biodiversity</i> ” in the section title with “ <i>synthetic biology</i> ”
73	8	Edit “ <i>pro-poor</i> ”. This is not a clear term.
74	23-32	Delete paragraph after the first sentence. The information in the paragraph is not relevant here - excessive detail.
74	34-40	Put CBD text in italics here and throughout the document where such text is cited.
75	7-9	Revise for factualness. This would only apply if the outcome was not an LMO within the scope of CBD Art8(g) or the Cartagena Protocol.
75	12-14	Revise for factualness. This is a general statement that is not supported by “ <i>as has been discussed earlier</i> ” for “ <i>many</i> ” applications.

75	14	The interpretation of “likely” and “significant” will be decided at national levels according to their circumstances (recall their sovereignty regarding environmental policies - Art2).
75	14-15	Revise for factualness. “...may also have to take into account the case of low-probability, high-impact scenarios which some synthetic biology applications may pose” Is there a credible reference for this statement?
75	17	Delete “negotiation” and replace with “development”
75	21	Put CBD text in italics here and throughout the document where such text is cited.
75	30-32	Put CBD text in italics here and throughout the document where such text is cited.
75	32	Insert “broad” after “this” at the end of the line
75	34	Insert “every term used in the definition of biotechnology, or in the obligations set out in Article 8(g), e.g. ...” after “define”
75	36-37	Delete sentence and replace with “However, it is generally accepted that synthetic biology falls within the CBD definition of “biotechnology”, and that Article 8(g) applies”. The reports of the AHTEG on Synthetic Biology should be referenced.
75	41	Insert “It also depends on whether or not the subsidiary agreement, the Cartagena Protocol on Biosafety to the Convention on Biological Diversity, applies (refer to relevant CP section).” as a new sentence at the end of the paragraph.
75	43	Insert after “organisms” the text “... (LMOs) but the definition can be found in the subsidiary agreement, the Cartagena Protocol. There is general agreement that most organisms developed through synthetic biology are LMOs as defined by the Cartagena Protocol”. Reference section 8.2.1 and reports of the AHTEG on Synthetic Biology.
75	44	Insert before “negotiators” the text “in the drafting of the Convention”
75	44	Delete “replaced the term” and replace with “chose to use the term LMO instead of”
75	44-45	Delete “with “living modified organisms”
75	45	Delete “to broaden the scope of obligations under the relevant articles (Glowka et al., 1994).” and replace with “to avoid terms already in use in national legislation. However, the two terms are considered functionally equivalent.” In practice, the terms are considered functionally equivalent, and this is indicated in the Secretariat FAQs: http://bch.cbd.int/protocol/cpb_faq.shtml#faq3 . Also: https://www.biodiversitya-z.org/content/living-modified-organism-lmo
75-76	46-47 1-3	Delete. “Unlike the Cartagena Protocol’s definition of living modified organisms, which applies to organisms obtained through the use of modern biotechnology, the Convention’s use of the term is meant to include organisms whose genetic material is modified through traditional techniques, such as selective breeding and artificial insemination, as well as “organisms whose genetic material is more directly modified through, for example, recombinant DNA technology” (Glowka et al., 1994).
76	7	Insert after “context of” the text “Article 8(g) of”
76	8	Replace “are” in “areas of research that are considered” with “may be”
76	19	Replace “may” with “is”; delete “be” before relevant
76	25	Insert “certain applications of” before “synthetic biology”

76	27-30	Delete the text <i>“One possible interpretation of this text is that two categories of risks are included – risks associated with the use of living modified organisms and risks associated with the release of living modified organisms. The text could also be interpreted to consider only those risks associated with both the use and release of living modified organisms.”</i> Please note that the text discussing the two possible categories of risk is unnecessarily complicated and confusing things. The “use” itself may be release.
76	32	Replace <i>“have been”</i> with <i>“are only”</i>
76	36-38	Delete sentence; the examples listed cannot be justified as examples of synthetic biology!
76	39	Delete <i>“significantly”</i> – this is speculative language
76	40	Delete <i>“genome edited animals and plant”</i> as this is not example of synthetic biology
77	2	Insert <i>“and the Cartagena Protocol”</i> after <i>“8(g)”</i>
77	7	Insert new text <i>“Therefore, a country has the right and not an obligation to regulate access to and use of their genetic resources, and ABS obligations will only apply if imposed under national ABS laws and as defined under such laws.”</i>
77	9-10	Delete sentence. The statement that this <i>“would give rise to an obligation”</i> is not necessarily correct- it depends on what the Party has chosen to implement (recall their sovereignty - line 5). This text (here and in sections immediately above) assumes that treaty provisions are directly applied verbatim in parties - this is not the case and is an inaccurate simplification.
77	13	Insert new sentence <i>“Although CBD Art 15 recognises sovereign rights of states and hence the key principle of ABS, the Nagoya Protocol further operationalises these principles and the actual ABS obligations are defined under relevant national law”</i>
77	21-22	Delete <i>“the access requirements of the Convention would, in general,”</i> and replace with <i>“ABS obligations under national laws might”</i>
77	27-28	Put CBD text and definitions in italics here and throughout the document where such text is cited.
77	33	Delete <i>“units of heredity distinguished genes from “junk” DNA.”</i> and replace with <i>“...units of heredity contain genes, i.e. distinguished genes “(sequences that encode proteins)” from “junk” DNA “(non-coding sequences)”</i>
77	34	Delete <i>“...understandings of heredity have changed dramatically; junk DNA is no longer considered “junk,” and functional units of heredity may need to be interpreted beyond the gene itself to include, for example, epigenetics which involve functional, and sometimes inherited, changes in the regulation of gene activity and expression that are not dependent on gene sequence (Ganesan, 2018; Gemmell, 2021) and which are increasingly implicated in linking genetics to the environment and disease (Cavalli & Heard, 2019).”</i> and replace with <i>“...understandings of both heredity and junk DNA have advanced and functional units of heredity may be interpreted beyond the gene itself.”</i> while retaining the relevant references from the original text. The text creates confusion regarding the scope of genetic material.
77	43	Delete <i>“types of value –“</i> Insert <i>“value”</i> after <i>“potential”</i>

77	43-44	Delete <i>“the state of art of technology as well as dynamic”</i>
78	2-4	Delete sentence. The ways of capturing value changes, not the genetic resource/material.
78	10-11	Delete <i>“– from DNA and RNA sequences to amino acid and protein sequences through to biochemical information –“</i> This suggests (and could pre-empt) types of digital information however a definition of “digital sequence information” has not been agreed.
78	19	Insert <i>“is currently an active area of discussion under the Convention and the Nagoya Protocol, as well as other international fora concerning genetic resources.”</i> after <i>“resources”</i>
78	19-38	Delete COP process and decisions are not as detailed in other sections of this document, and this information does not provide any clarity on the topic.
78-79	40-42 1-25	Delete text in section (b) <i>Genetic resources originating from synthetic biology</i> Synthetic biology applications may use genetic resources, but the resulting products are not themselves genetic resources. Just because they contain genetic material, they are not a genetic resource in the scope of the CBD/NP. This whole section is confusing and misleading and should be deleted. Alternatively, it should be explicitly stated that synthetic biology products are not genetic resources (this is not "another open question"). Note that synthetic biology applications may use genetic resources, but the resulting products are not themselves genetic resources. Just because they contain genetic material they are not a genetic resource in the scope of the CBD/NP. The products resulting from synthetic biology are man-made and as such are not a genetic resource over which states can claim sovereign rights (how to define a country of origin where these resources can be found <i>in situ</i> – there is no such thing as a country where they have acquired properties through influence of the natural surroundings in which they occur).
79	27-28	Delete <i>“A number of COP decisions (e.g. COP Decisions XI/29, XII/2 B, XIII/23 B and 14/24) have sought to implement”</i> and replace with <i>“The Convention includes provisions on...”</i>
79	28	Delete <i>“pursuant to”</i> and replace with <i>“in”</i>
79	28-29	Delete <i>“of Convention”</i>
79	38-41	Put treaty text in italics
80	9-10	Delete <i>“holding that Parties shall”</i> and replace with <i>“obliging Parties to”</i>
80	10-12	Put treaty text in italics
80	17	Suggested edits to place the paragraph into the context of the section. Delete <i>“a useful proxy”</i> and replace with <i>“an”</i> Insert <i>“activities”</i> after <i>“R&D”</i> Insert <i>“around the world.”</i> after <i>“synthetic biology”</i> Delete <i>“by 2017”</i> and replace with <i>“In the work of Shapira et al (2017), a bibliometric search approach was developed to identify scientific papers published in this domain, and provide insight on patterns of international spread, funding, and disciplinary contributions”.</i>
80	18	Insert <i>“Their approach revealed that...”</i> before <i>“more than”</i>

81	14	This section is missing comment on the Nagoya Protocol and its explicit recognition of traditional knowledge associated with genetic resources.
81	44	Insert “two” before “subsequent meetings”
82	4	Replace “living organisms” with “LMOs”
82	2	Insert "on the topic of risk assessment and risk management" at the end of the sentence.
83	2	Refer to the legal basis for the Cartagena Protocol - Art 19(3) of the Convention.
83	18	Insert new sentence after “modern biotechnology.” "The Cartagena Protocol defines the terms "living organism" (see p 76, lines 4-6) and "modern biotechnology" (p. 85)." Provide references to these in the text. Given the statement made in the sentence that follows, there needs to be clear direction to the definition of "modern biotechnology".
83	23	Replace “living modified organisms” with “LMO” and use this abbreviation consistently throughout
83	24	Delete “inform the question of whether a synthetic biology organism falls within or outside the Protocol’s definition of “living modified organism” and replace with “inform this question.”
83	27	Replace “living modified organisms” with “LMO” and use this abbreviation consistently throughout
84	3-15	Replace “living modified organisms” with “LMO” and use this abbreviation consistently throughout
84	17-20	The information presented is repeating earlier text. Please refer back and shorten this text.
84	24	Please delete “outstanding questions” and replace with "questions that may arise" since these are not outstanding questions.
84	25	Delete “organisms” and replace with “LMOs”.
84	30-31	Delete “seem to primarily”. It is clear that the Cartagena Protocol concerns processed materials, all three instances state: “... products thereof, namely, processed materials that are of living modified organism origin, containing detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology.”
84	35-41	This paragraph should include comment that the processed products will be subject to other applicable product-based regulatory regimes, e.g. food, chemicals, pharmaceuticals.
84	43	Delete “The situation is less clear with regard to DNA and constituent parts”. The situation is not unclear - these are not LMOs.
84	46	Delete “synthetic biology” and replace with "use in biotechnology".
85	4	Delete “may not” and replace with “do not”. Such DNA cannot be defined as an LMO.
85	6-10	Delete this paragraph. The text above (p 83, line 19) states that the definitions are "intrinsically interlinked", and here they are being separately analysed and applied in a way that expands their scope. A piece of DNA in isolation is not living or able to replicate. This "DNA and constituent parts" section as a whole is unnecessary.
85	11	Delete “however”.
85	14	This “novel combination” section is (again) considering definitions in isolation.

85	15	Delete “ <i>can result from</i> ” and replace with “ <i>is not a defined term, but one interpretation is that it may be ...</i> ”.
		The suggested edition is required as this is only the view of the paper cited. Another view is that "novel combinations" result from recombinant DNA techniques and the resulting integration of recombinant DNA (usually a transgene) and this is often the interpretation under national biosafety regulations. Another view is that a novel combination does not need to be limited to "functional units of heredity". To be more balanced, these alternative views should be presented and should also include the interpretation provided by regulatory bodies in different LATAM countries as part of exclusion of genome editing outcomes from the scope of GMO regulations. Note that these interpretations differ from and supersede the one referenced to Mackenzie 2003.
85	16	Please note that Mackenzie 2003 is not in the reference list.
85	21	Delete “ <i>would</i> ” and replace with “ <i>may</i> ”.
85	23	Delete “ <i>would likely still</i> ” and replace with “ <i>may</i> ”.
85	24	Delete “ <i>because</i> ” and replace with “ <i>where</i> ”.
85	24	Delete “ <i>could</i> ”.
85	44	Delete “ <i>may</i> ” and replace with “ <i>would</i> ”.
86	15	Insert “ <i>of an LMO</i> ” after “ <i>movement</i> ”.
86	44	Delete “ <i>The Parties</i> ” and replace with “ <i>Ad Hoc Technical Expert Groups on Risk Assessment</i> ”. The Parties have never endorsed or adopted what the AHTEGs developed.
87	8	Replace “ <i>living organisms</i> ” with “ <i>LMOs</i> ”.
87	11	Delete the two sentences starting from “ <i>In addition...</i> ” This example is an LMO, there are transgenic examples of this. There is no reason why Annex III cannot still apply.
87	16-23	Delete this paragraph. There is a lot of unnecessary detail here.
87	24	Delete “ <i>more recently in</i> ” and replace with “ <i>For LMOs developed through synthetic biology, questions have been raised concerning the ongoing applicability of the Cartagena Protocol's risk assessment procedures. These questions have focused on challenges with the long-established comparator approach, and knowledge gaps regarding assessment of ecological impacts where the application is unprecedented.</i> ”
87	25-26	Delete “ <i>recognised the divergence in views among Parties on whether or not additional guidance on specific topics of risk assessment is needed. The COP-MOP</i> ”.
87	28-30	Delete “ <i>establish a process for the identification and prioritisation of specific issues regarding risk assessment of LMOs with a view to developing further guidance on risk assessment on the specific issues identified, and to</i> ”.
87	31-32	Delete “ <i>and living modified fish</i> ”.
87	35	Replace “ <i>living modified organisms</i> ” with “ <i>LMOs</i> ”.
87	36	Delete “ <i>with a view to enabling the Subsidiary Body to</i> ” and replace with “ <i>who will then</i> ”.
87	40	Delete “ <i>were still to be held</i> ” and replace with “ <i>are in progress (Feb 2021, May-Jul 2021)</i> ”.
87	46	Insert “ <i>as described in the section above</i> ” after “ <i>assessment</i> ”.

88	3	Replace “ <i>Advance Informed Agreement</i> ” with “ <i>AIA</i> ”.
88	15	Delete “ <i>also left</i> ”
88 89	20-43 1-10	General comment – the majority of the text in the “contained use” section is devoted to describing issues or concerns raised by certain interest groups. There needs to be a more balanced review of the subject that also reflects established practices for biosafety under containment. We make specific editing recommendations to address this. We also note that the same issues are raised in the Technical Series document of 2015 – therefore, this text is not an “update”
88	20	Delete “ <i>At least three</i> ”
88	21	Delete “ <i>First</i> ”
88	23	Insert “ <i>certain</i> ” before “ <i>organisms</i> ”
88	24	Insert new text “ <i>This call for containment strategies for organisms resulting from synthetic biology techniques that are different to those applied for LMOs however is questionable. This is because, in line with Article 18 of the Protocol, containment practices (i.e. risk management and mitigation) are based on a risk assessment and, as such, are tailored to minimize the risk to biodiversity and human health</i> ”.
88	24-25	Delete the sentence “ <i>Importing countries may need advance information in order to “judge the effectiveness of available containment (Ibid)”</i> ”
88	27-31	Revise for completeness. Several edits are recommended, resulting in the following rewrite of the paragraph: “ <i>EcoNexus, a European civil society group, does not consider DIYbio (do-it-yourself biology)/citizen science individuals and collectives as being able to provide for “contained use” and is concerned that AIA “might become close to impossible” in such instances (EcoNexus, 2011). Conversely, different reports on DIYbio found that few DIYers are using “sophisticated” synthetic biology, and most work in labs that are rated as Biological Safety Level 1, in a transparent and responsible manner (Grushkin et al., 2013; Landrain et al., 2013; Seyfried et al., 2014; Kuiken, 2016). Several developments involving self-regulation by the scientific community which are relevant to the DIYbio discussion are considered in Section 7.3</i> ” Added reference: Kuiken (2016). Governance: Learn from DIY biologists https://www.nature.com/articles/531167a/
89	1-10	Delete this paragraph. This is not relevant to synthetic biology. If any part of the paragraph is retained, it should be limited to the final three lines: “ <i>Concerns have been expressed that diverging regulatory or ethical</i> ”.
90	1-3	Delete these lines, they are incorrect - their use as pharmaceuticals will be highly regulated (“addressed”). They will also be regulated as LMOs. There will be more than one regulatory agency with responsibility.
90	26	Delete “ <i>to</i> ” and replace with “ <i>may</i> ”.
90	30	Insert “ <i>the</i> ” before “ <i>potential</i> ”.
90	32	Insert “ <i>, in accordance with a risk assessment (Article 15).</i> ” after “ <i>health</i> ”.
90	32	Delete “ <i>addresses the extent to which Parties are entitled</i> ” and replace with “ <i>provides for Parties</i> ”. Article 26 does not specify the “extent”, it just states that Parties “may ..., consistent with their international obligations”.

90	34	Insert “ <i>should they choose to, and consistent with their other international obligations</i> ” after “ <i>IPLCs</i> ”.
91	33	Insert “(Article 1 - Supplementary Protocol)” after “organisms” at the end of the sentence.
91	37	Insert “ <i>With respect to intentional transboundary movements,</i> ” prior to “ <i>It applies</i> ”.
92	25-29	Delete “ <i>Further, as described in Section 4 of this document, it is possible that LMOs resulting from synthetic biology techniques could cause adverse effects on the conservation and sustainable use of biological diversity. For example, unintentionally released organisms may transfer the inserted genetic material and thus change biodiversity at a genetic level, intentionally released organisms may become invasive due to engineered fitness advantages.</i> ” and insert “, and require assessment of their potential adverse effects on biological diversity. Concerns associated with these LMOs, as for LMOs that have preceded them, include gene flow and increased invasiveness and persistence.” directly after “Protocol”. This suggested edit uses more neutral (less presumptive) language.
92	30	Insert “, which are LMOs in the scope of the Cartagena Protocol,” after “gene drives”.
92	30	Delete “ <i>the</i> ” prior to “ <i>environment</i> ”.
92	30-31	Delete “ <i>of such organisms</i> ”.
92	32-34	Delete “ <i>As has been discussed, there appears to be significant controversy as to the scope and therefore “significance” of the potential damages. The applicability of the provisions of the Supplementary Protocol would have to be assessed for particular cases</i> ” and replace with “ <i>The implications, in terms of determinations of “damage” according to the provisions of the Supplementary Protocol, and its measurability and significance, have not yet been extensively examined.</i> ” The suggested edit uses more neutral language because the “controversy” in this context is overstated.
93	4-12	Put treaty text in italics.
93	4	Delete “ <i>addresses the use of terms in the Protocol. It</i> ”
93	5	Delete “ <i>s</i> ” from “ <i>Articles</i> ”.
93	6	Delete “ <i>It</i> ” and replace with “ <i>Additionally, the Nagoya Protocol</i> ”.
93	18	Delete “ <i>synthetic biology</i> ” and replace with “ <i>genome editing</i> ”.
93	19	Delete “ <i>food and feed</i> ” and replace with “ <i>crops</i> ”.
93	19	Insert “ <i>being examined, are...</i> ” prior to “ <i>under</i> ”.
93	19	Delete “ <i>advance</i> ”.
93	20	Insert “ <i>Using the example of sugarcane, ...</i> ” prior to “ <i>If</i> ”.
93	20	Delete “ <i>of sugarcane</i> ” after “ <i>this use</i> ”.
93	21	Insert “ <i>on its genetic and biochemical composition</i> ” after “ <i>research</i> ”.
93	23	Delete “ <i>interpreted as</i> ”.
93	24	Delete “ <i>would</i> ” and replace with “ <i>may</i> ”. This would depend on the requirements of the provider.
93	24	Delete “ <i>and</i> ” and replace with “ <i>where</i> ”.

93	25	Replace “implementing” with “implement” Delete “obligations”.
93	32-33	Delete “The use of these synthetic biology techniques raises questions as regards to until what extent the results of modifications of a natural genetic resource continue to be subject to the benefit-sharing obligations.” and replace with “While not unique to synthetic biology, a question that arises is the extent to which a genetic resource continues to be subject to benefit sharing obligations, particularly where it undergoes multiple (subsequent) applications and modifications.”
93	35-36	Delete “It also provides that “such sharing shall be upon mutually agreed terms”.
93	37	Insert “This is facilitated, where applicable, through the use of mutually agreed terms that include terms on subsequent third-party use (Article 6(g)(iii) - Nagoya Protocol.” at the end of the paragraph after “(Ahrén et al., 2012)”.
94	2	Refer to where the definition of derivative is provided above instead of repeating it here.
94	13	Insert “However, the synthetically produced enzyme is not the “naturally occurring” biochemical compound per the definition.” at the end of the paragraph after “(Erickson et al., 2011)”.
94	15-18	Delete the sentence. “A separate question might be whether access to derivatives of organisms resulting from synthetic biology techniques – such as isoprene – would also be covered by the Nagoya Protocol (see similar discussion on access to genetic resources originating from synthetic biology in Section 8.1.5.)”. This is confusing scope and is misleading.
94	19-23	Move this paragraph up to line 7 and attach it to the 2nd paragraph.
94	25	Insert “derivatives, and” prior to “access”.
94	25	Insert “any” prior to “benefit-sharing”.
94	25	Delete “in relation to derivatives”.
94	27	Delete “until which extent of” and replace with “where in..”.
94	29	Insert “, where applicable...” after “derivatives”.
94	36	Insert “the scope of” after “beyond”.
94	37	Insert new sentence “It is also recognised that more than one international instrument may be relevant, and consequently there can be multiple national laws and regulations, and overlapping legal responsibilities at national levels.” prior to “This”.
95	7-8	Delete “Limited analysis is available concerning potential gaps in international governance. Additionally, this update”. This very topic has been discussed extensively in the synthetic biology work programs of the CBD which implies that extensive analysis is available.
95	8	Insert “Table 2 below” prior to “prioritises”.
95	15	Delete “related to the work of the CBD” as not all examples are related to the CBD.
96	4	This section should refer to the following documents: World Health Organization. Guidance Framework for Testing of Genetically Modified Mosquitoes. Geneva: World Health Organization, 2014. World Health Organization. Guidance Framework for Testing Genetically Modified Mosquitoes, Second Edition. Geneva: World Health Organization, 2021.
96	14-15	Delete “which were not intended to be mutually exclusive”.
96	17	Insert “laboratory” after “a”.

98	14-21	The WHO/TDR and FNIH foundational <i>Guidance Framework for Testing Genetically Modified Mosquitoes</i> of 2014, and the 2021 second edition that also includes gene drives should be included here.
99	17	The information in this part is relevant to the section on contained use and it should be mentioned there, and that section referred to here.
99	21	Insert “ <i>in a laboratory (i.e. contained use) setting</i> ” at the end of the sentence after “ <i>trends in biosafety</i> ”.
99	21	Insert “ <i>Although focusing on human health aspects primarily,</i> ” prior to “ <i>The Laboratory Biosafety Manual...</i> ”
99	24	Delete “ <i>the third edition</i> ” with “ <i>previous editions</i> ”.
99	25	Replace “ <i>The WHO asserts</i> ” with “ <i>It reinforces the idea</i> ”.
99	26-27	Replace “ <i>and that this novel</i> ” with “ <i>Further, such</i> ”
99	27	Replace “ <i>will allow</i> ” with “ <i>allows for</i> ”
99	32	Delete “ <i>synthetic biology,</i> ”.
99	35-37	Delete the sentence “ <i>However, countries ... life science research</i> ” and replace with “ <i>In that same section, the WHO also advises to not focus on any one of these emerging technologies but rather use one framework in which risks can be assessed and managed regardless of the technology involved</i> ” This is more relevant content to include, as it advocates for a holistic approach using the already available frameworks (instead of additional separate legislation/processes etc.).
100	3-14	Revise to remove duplicated text. The paragraphs should be merged to remove duplicated text.
100	8-9	Delete the first sentence of the paragraph as it repeats lines 4-5.
100	13	Delete “. <i>It</i> ” after “ <i>Member States</i> ” and replace with “ <i>and it</i> ”.
100	14	Delete “ <i>when it was unanimously adopted by the Sixty-fourth World Health Assembly</i> ”. This was already stated on line 3.
102	30	Insert “ <i>conservation</i> ” prior to “ <i>challenges</i> ”.
104	13	Insert “ <i>do not</i> ” prior to “ <i>determine</i> ”.
106	7	Insert “ <i>environmental</i> ” prior to “ <i>impacts</i> ”.
106	8-12	Delete “ <i>through economic, social, and cultural impacts. For example, as considered in Section 4.1. above, depending on the engineered gene drive system, theoretically, a genetic modification could spread through target populations (non-localised) and persist indefinitely (self-sustaining), or be restricted in spread (localised) or persistence (self-limiting). Direct impacts on the transboundary environment, however, would depend on the specific application of synthetic biology.</i> ”. The “ <i>example</i> ” is not about this, and the section is about the environment.
106	12-15	Delete “ <i>Currently, intentional environmental release of organisms resulting from synthetic biology techniques seem to be limited to a few instances such as commercially available soya bean engineered to obtain a high-oleic oil and engineered insects which contain a self-limiting gene resulting in either a reduction in the pest insect population that spread disease</i> ” These are not examples of synthetic biology.
106	15	Delete “ <i>either</i> ” and “ <i>pest</i> ”

106	26	Insert “, however the definitions of the Supplementary Protocol (refer to section) provide guidance in the context of LMOs.” after “damage”.
106	32	Insert “In the Supplementary Protocol, a causal link is required between the damage and the LMO (Article 4).” after “species”.
106	36-37	It is misleading to state that required measures are not clear – for synthetic biology, the measures are codified in CBD Article 8(g) and the Cartagena Protocol.
107	7-8	Delete “in particular potential impacts of very low probability but very high magnitude.”.
107	26	Insert “reflecting different levels of acceptance of risk” after “assessed”.
107	28	Insert “compared to existing LMOs and applications of biotechnology” after “novel risks”.
107	28	Delete “knowledge” and replace with “accumulated knowledge and expertise”.
108	4	Insert “those that are of” before “low probability” Replace “and” before “high-consequence” with “but potentially”
108	25	Insert “the notion of” before “precaution”
112	21-23	Delete “which defines genetic resources as genetic material of actual or potential value, and genetic material as any material of plant, animal, microbial or other origin containing functional units of heredity” This information has been provided already several times.
112	26	Replace “synthetic biology” with “genome editing”
112	27	Replace “as is” with “and this includes”
114	36	Delete “existing”
115	5	Replace “particularly” with “including”
115	7	Replace “modalities for access and benefit sharing” with “marine genetic resources, including questions on the sharing of benefits.” The suggested edit is the draft treaty section title.
115	9	Delete “modalities for”
115	34	Insert “traditional knowledge associated with” before “GRs”
116	21-30	Please edit text to reflect that patents are also very relevant to the enabling technologies and tools.
116	22	Insert “in their national regimes” before “for” at beginning of the line
116	38	Replace “applying them” with “defining them at the national level”
117	10-11	Replace first sentence with “Enabling technologies and tools, components, organisms, and products resulting from synthetic biology techniques may fulfil the necessary criteria and may be the subject of patents in one or more jurisdictions”
117	11	Delete “In particular”
117	23	Insert “potentially” before “be excluded”
118	32-36	Combine under one bullet point text beginning with “defined by the expression....” and finishing with “...propagated unchanged”
121	31	Delete “of”.
121	32	Replace “leading” with “may lead to”
121	34	Insert a full stop after “DNA”.

121	40	Provide fuller reference, it is not clear that this is referring to the 2015 synthetic biology technical series no. 82.
121	42	Replace “causing” with “having the potential to cause...”
121	43	Insert at the end of the sentence additional text “, however in this example the measures were ultimately not successful.”
122	1	Keep consistent , “Biotech” is referred on previous page as “EC-Biotech” (no italics)
122	32-34	Delete sentence “At this point.....often invoked”. This is inconsistent with other segments in the text. The inclusion of this statement raises the question why there is such a strong focus in the text to genome editing in agriculture? Please also note that the primary use of crops is for food and feed.
122	36	Revise for completeness. The text stating “outdoor ponds of algae ... may be accessible to wildlife”. Such ponds would likely be contained in some way, e.g. they would be subject to specific risk management containment measures identified as part of a case-by-case risk assessment (e.g. suitable fencing to keep wildlife out).
123	27	Insert “defined as” before “living plants”
124	7	Delete “for the case of living modified organisms”
124	9	Delete “rather”
125	1-2	Delete: “and in terms of possibly producing adverse health effects”.
125	13-20	Please clarify text to reflect that these standards are generally the basis of food safety regulation, which includes foods derived from LMOs.
125	33	Replace “apply” with “be relevant”
125	38	Replace “apparent gaps and overlaps associated to the l” with “aspects of the”. It is inevitable that different synthetic biology uses and outcomes are regulated under different regulatory frameworks, that may or may not overlap, depending on the nature of the product and its intended use. Please make it clear in the text that there will be more than one regulatory regime that is applicable to any given product and/or use of synthetic biology. As it reads now, it appears that the authors are making an assumption that this should not be the case, i.e. that only a single regulatory regime is appropriate.
125	38	Insert “and the ...” after “synthetic biology”.
125	39-40	Delete “associated to this scenario are also discussed”.
126	2	Insert “nor is it exceptional” after “duplication”.
126	3	Replace “discussed or considered under” with “within the scope of”.
126	4	Insert “considered” after “but”.
126	7	Delete “Although synthetic biology is often referred to as a single discipline, the”. This is not correct (see previous comments on the same statement).
126	8	Insert “of synthetic biology, the unclear distinction between synthetic biology and “older” biotechnology that is the foundation of synthetic biology, and the numerous areas of research that are included as synthetic biology in this document...” after “definition” and delete “and the numerous areas of synthetic biology research”.
126	14	Insert “Rather, there is an” after “biology” and delete “The”.
126	14	Insert “collection of” after “extensive”

126	14	Insert " <i>that potentially</i> " after " <i>mechanisms</i> ".
126	16	Delete " <i>the rapid pace of</i> ".
126	19-20	Delete " <i>and therefore, they were not developed with the necessary scope and scale that some of the potential impacts of synthetic biology may present.</i> " and replace with " <i>and while it is possible that they may not presently provide the necessary scope to address some of the potential impacts that synthetic biology may present in the future, such limitations were not clearly identified in this review</i> ". The conclusion of the authors cannot be made on the basis of the term "synthetic biology" not being used, when they have basically used it themselves as a replacement term for "biotechnology", which is defined, and for which there are established regulatory mechanisms. The text needs to be factual and balanced.
126	21	Replace " <i>fragmented</i> " with " <i>complex</i> ".
126	37	Delete " <i>upstream</i> " and " <i>market ready</i> ".
127	5	Replace " <i>offers</i> " with " <i>elaborates</i> ".
127	4-7	Revise to clarify that the Cartagena Protocol is not limited to the risk of harm "caused by the transboundary movement of LMOs". It applies to the safe transfer, handling and use of LMOs, with specific focus on transboundary movements (Art 1). Generally, regulators will apply the same risk assessment processes irrespective of whether or not a transboundary movement precedes the use .
127	10	Replace " <i>its Nagoya – Kuala Lumpur</i> " with " <i>the</i> " since this has been abbreviated to " <i>Supplementary Protocol</i> " previously.
127	22	Replace " <i>synthetic biology, a closer examination concerning</i> " with " <i>biotechnology more generally, consideration of</i> ".
127	23-24	Replace " <i>appears likely and this will likely take into consideration of</i> " with " <i>will likely continued to be monitored and</i> ".
127	24	Insert " <i>may be relevant to consider, with the potential for greater collaboration in the future.</i> " after " <i>Protocols</i> ".
127	33	Replace " <i>were</i> " with " <i>maybe</i> ".
128	1-2	Revise for completeness. We question the conclusion of the authors about gaps due to the lack of a treaty regime. National governments are and will be able to determine if additional regulatory oversight is necessary.
128	9-10	Delete " <i>somehow implies that there could be potential interactions amongst various organisations in relation to</i> " and replace with " <i>suggests that it would be beneficial for the international organisations with overlapping mandates to collaborate in relation to ...</i> ".
128	14	Replace " <i>can</i> " with " <i>could potentially</i> ".
128	16	Insert " <i>public</i> " after " <i>biology</i> ".
128	17	Insert " <i>LM</i> " before " <i>mosquitoes</i> ".
128	28	Delete " <i>s</i> " from " <i>haves</i> ".
128	34	Insert " <i>the strong participation of the conservation community, and</i> " after " <i>given</i> ".
128	38	Insert " <i>Policy development by the IUCN is likely to influence synthetic biology discussions under the Convention and its Protocols</i> " after " <i>governance</i> ".
128	43	Insert " <i>under these treaties</i> " after " <i>underway</i> ".
128	44	Insert " <i>(if any)</i> " after " <i>obligations</i> ".

128	45	Insert "the tools and technologies used in " after "for".
128	45	Insert "the resulting" after "biology".
128	45	Replace "developed using" with "that use".
129	3	Insert "under UNCLOS" after "jurisdictions".
129	4	Delete "on this issue.".
129	10	Delete "also".
129	16	Insert "specifically, "after "biology"
129	22	Insert "those developed by" after "such as".
129	23	Delete "significant".
129	29-47	Delete This section should be deleted because it is redundant with Section C. In the first paragraph, the comment on sequencing has already been made elsewhere in the text. The "knowledge gap" referred to in the second paragraph (lines 34-37) simply reflects that this is an evolving area of science, not a mature field. The comment about "delivering on its promise" (line 33) is pointless. If there is such view, it is the result of the sensational language used in connection to synthetic biology. The oft-repeated "rapid pace of development" is an example of this - there is no justification for this claim. This is, in our view, supported by the factual examples presented in the report which show that there is very little "synthetic biology". The computing information in the third paragraph (lines 38-47) should be moved into the "supporting technologies and tools" section (Section C starting on page 16).
130	2	Replace "are as equally" with "may be as".
130	2	Insert "in some countries" after "important".
130	4	Insert "advanced stages of development or" after "that".
130	5	Revise the comment "relatively little real-world data" – there is ample relevant real-world data for existing LMOs, including SEC benefits.
130	8	Replace "classical" with "applications of" Delete "and associated concerns"
130	9	Delete "has been somewhat absent" and replace with "has not been visible". Although benefits many not be assessed under the GM risk assessment in many countries it does not mean it is absent.
130	9-10	Delete "a situation exacerbated by the lack of agreed international standards with respect to the types of data to collect, and how, for each type of application."
130	13	Delete "socio economic and political".
130	13	Delete "very".
130	41	Replace "concerns" with "involves".
130	42	Please clarify the term "non-traditional"?
130	44	Insert "the" before "research".
131	2	Delete "real or apparent".
131	3	This line mentions "independent". It should be noted that the developer being a source of information is not an issue if there is transparency. Some role for developers in providing information will be needed because they will have the most scientific expertise about the project and are generating information following regulatory requirements for data generation in support of their applications.

131	7-12	There are more examples of community participation that could be mentioned here, and it could also be mentioned that community participation is not limited to developing countries or IPLCs. An often-cited example (amongst others) that provides a basis for LM mosquitoes containing engineered gene drives is that undertaken for releases of <i>Wolbachia</i> infected (non-LM) mosquitoes in northern Australia.
131	18	Replace “ <i>And</i> ” with “ <i>Also</i> ”.
131	21	Delete “ <i>moving</i> ”.
131	21	Delete “ <i>to</i> ” from “ <i>into</i> ”.
131	31	Replace “ <i>of</i> ” with “ <i>and</i> ”
131	34	Replace “ <i>predominantly with research, handling, release and standards</i> ” with “ <i>with containment measures and release procedures.</i> ”
131	37	Delete “ <i>far</i> ”.
131	36-38	Revise for factualness. There is no evidence to support multiple elements of this sentence: “ <i>The rapid advancement of the underlying sciencethe exponential rise in potential applicationsfar exceeding the speed at which national and international governance frameworks can adapt</i> ” This over-stated language is not balanced or factual.
131	40-44	Regarding the “ <i>challenge will be in arriving at international consensus</i> ”. International consensus and international rules are not always necessary - international instruments provide an internationally agreed frameworks/guidelines/recommendations etc. but ultimately countries will determine what and how they want to regulate.
131	42-44	Delete “ <i>As in the case of challenges arising from the differences between a product-based and a process-based approach to regulation for classical genetic engineering, it is to be expected that similar if not greater challenges will continue to be faced for those organisms resulting from synthetic biology.</i> ” and replace with “ <i>It is expected that challenges arising from differences in regulatory approaches for biotechnology (e.g. process-based versus product-based) will continue to be faced for those organisms resulting from synthetic biology.</i> ”
132	7	Delete “ <i>commercial deployment and</i> ”
132	13	Insert “ <i>likely</i> ” after “ <i>will</i> ”.
132	13	Insert “ <i>more than one</i> ” before “ <i>national</i> ”.
132	13	Insert “ <i>who will need to work together</i> ” after “ <i>authorities</i> ”.
132	14	Insert “ <i>consistent with international recommendations for the development of these LMOs (e.g. NASEM 2016, WHO guidance framework 2014, 2021).</i> ” after “ <i>stepwise approach</i> ”,
132	17	Insert “ <i>efficacy with regard to its intended public health use</i> ” after “ <i>demonstrate</i> ”.
132	17-20	Delete “ <i>a positive impact for disease control. Such diverging orientations could pose practical challenges in the design of field evaluations of engineered gene drive organisms, especially when aiming to minimise risk while demonstrating positive health impacts.</i> ” This is creating/overstating a problem - these objectives are not mutually exclusive. Any field evaluation of an LMO is for a particular purpose, and it can be designed

		according to more than one regulatory requirement. Addressing different regulatory assessment end points is not that hard in practice.
132	19-22	Replace the following sentences <i>“It shows that issues of interaction and coordination are potential shortcomings under a fragmented international regime. Such shortcomings have the potential to be further perpetuated and exacerbated by the absence of”</i> with: <i>“It shows that interaction and coordination amongst different regulatory agencies with overlapping responsibilities will be required.”</i> Note: The use of <i>“fragmented”</i> in line 21 is misleading. It is not "fragmented", there are just multiple regimes to comply with depending on the application. This is not unusual. e.g. a GM crop field trial may require coordination between LMO regulators, pesticide regulators, and/or therapeutic goods regulators.
132	22	Insert <i>“This situation could be assisted by”</i> prior to <i>“integrated guidance provided under each regime or implementation under national law.”</i>
132	25	Please provide references to the two WHO recommendation documents.
132	26	The discussions under the CBD and Protocols referred to will be duplicative and redundant unless there is coordination with the WHO on mosquitoes
132	44	Delete <i>“exponentially”</i> as there is no evidence for this in this document.
132	44	Insert <i>“under research, in development, or”</i> after <i>“applications”</i> .
132	45	Delete <i>“solve”</i> and replace with <i>“contribute to addressing”</i> .
132	49	Replace <i>“become available”</i> with <i>“are envisioned”</i> .
133	3	Replace <i>“shown significant growth”</i> with <i>“grown”</i> .
133	3	Delete <i>“goes in line”</i> and replace with <i>“is consistent”</i> .
133	7	The genome edited soybean product referred to is not an example of synthetic biology.
133	8	The self-limiting insects referred to are not an example of synthetic biology. They are “classic” LMOs that are assessed under existing regulatory frameworks. The first generation of these were developed in 2002, with field trials conducted before the 2015 synthetic biology technical series.
133	9	Delete <i>“advanced stages of”</i> . These are not advanced when still completely in small-scale contained experiments.
133	9	Delete <i>“genome edited animals and”</i> as these are not examples of synthetic biology.
133	12	Delete <i>“and”</i> and replace with <i>“will progress to”</i> .
133	12	Delete <i>“and development”</i>
133	14	Delete <i>“Despite”</i> and replace with <i>“With”</i>
133	14-20	Delete this entire paragraph For the first two sentences (lines 14-16) – Is this really necessary on a general scale? Possible impacts will be discussed on a case by case basis. For the last sentence (lines 16-20) – as we have already commented, the term synthetic biology means the same thing as pre-existing "biotechnology" language. The scope of synthetic biology presented in this paper is as broad as possible, and still there are no examples that are outside the scope of existing regulatory mechanisms.
133	25	Insert <i>“legislation and”</i> after <i>“existing”</i> .
133	27	Delete <i>“some of”</i> .

133	28-29	Delete “ <i>the inability to potentially detect and identify the applications of synthetic biology</i> ” and replace with “ <i>challenges with detection and identification of certain organisms discussed in this document.</i> ”
133	30	Insert “ <i>However, implementation and capacity challenges are not unique to synthetic biology and are the subject of extensive discussion under the Convention and Cartagena Protocol.</i> ” at the end of sentence after “ <i>developed</i> ”.
133	32	Delete “ <i>international regimes as silos and the need to firstly better integrate/coordinate governance of synthetic biology and secondly, to expand the focus of the governance</i> ” and replace with : “ <i>international regimes as silos, perhaps taking an overly simplistic view that if a specific international regime does not exist then regulation must be absent. This is misleading. The example given above for LM mosquitoes containing engineered gene drives highlights the need for relevant international regimes to collaborate on issues of overlapping concern.</i> ”
133	33	Delete “ <i>to expand the focus of the governance</i> ” and replace with “ <i>We also assert that the focus of governance should be expanded</i> ” It needs to be made clearer that this is the view of the authors.
133	35-47	The content in this paragraph following “ <i>Responsible research and innovation</i> ” is all new information, it belongs in the main body of the document, not the “conclusions”.
134	2	Provide a weblink in footnote for COP decision 14/19
134	3-12	This paragraph is new information, relevant to section 10.6 -it should go there, not in the “conclusion”. Lines 3-4 need to include references to the cited work.
134	21	Replace “ <i>form</i> ” with “ <i>from</i> ”
134	29-43	The conclusion section is too long - too repetitive, and too much new information is introduced. It should be a clearly written summary. Specifically, the paragraphs running from lines 29-38 and 39-43 are repetitive and unnecessary. In addition, in line 43, there is a suggestion that certain international laws are ill-equipped? What specifically makes them “ill-equipped”? this is not demonstrated in this document which merely reviews (does not assess or evaluate) legal provisions.
135	8-11	Delete these two sentences. What “gaps” are referred to here? The only “gap” might be national implementation, which is not specific to synthetic biology.
135	13	Delete “ <i>solving</i> ” and replace with “ <i>providing new tools and approaches for addressing</i> ”.

Please submit your comments to secretariat@cbd.int.