Comments on the study on concept and scope – Governments				
Country	**Page #**	**Line #**	**Comment**	**Action taken and comments**
Canada	0	0	"Off target effects. The analysis of potential risk of off-target effects does not fully place the potential risk of off-target effects into the larger context of genetic changes that may occur through spontaneous or conventional breeding, nor does it indicate how off-target effects can be observed and mitigated. Please see Schnell et al, 2014: A comparative analysis of insertional effects in genetically engineered plants: considerations for pre-market assessments | SpringerLink Although this paper does not deal with synthetic biology applications, it does present a discussion around the spontaneously occurring genetic changes that happen in plants (transposons, NHEJ, conventional breeding, etc) and a summary of risk assessment of positional effects as unintended genetic changes. For example, the following excerpts regarding mitigation of risk from Schnell et al, 2014 may provide more context: "As has already been discussed, the relationship between genotype and phenotype is complex and it is also tempered by the environment. Genetic changes may be introduced into plants spontaneously or through conventional breeding or genetic engineering. The buffering capabilities of plant genomes and the quality control systems in plant cells will prevent many of these genetic changes from giving rise to discernible changes in a plant's phenotype." "Cultivar development typically requires upwards of 10 years and involves the evaluation of thousands of plants, resulting in the selection of one or very few final cultivars. Throughout breeding and seed production, selection is applied to eliminate off-types, which are those plants that show an unintended trait." "The processing and preparation of foods and feeds may also play a role in managing the risks associated with genetic changes. For example, processing conditions that involve heat or pressure may significantly reduce the levels of toxins and/or anti-nutrients in the food or feed before	General comment noted. Revision made.

			consumption, so that any genetic changes that alter the levels of such compounds do not present a safety concern.”"	
Republic of Korea	0	0	"As a scientist studying in the field of synthetic biology, I was happy to review this kind of technical series on synthetic biology. Most of all, I have concerns about the definition and scope of synthetic biology (SB) in the current draft. I think CBD provided the broad definition and scope of SB (page 8, lines 9-12), which makes the lack of certainty about whether SB is a single discipline or multi-disciplines, how SB impacts society, and the environment, and how market value and growth rate of SB are estimated. SB should be distinguished from conventional genetic engineering that has been generating classical GMOs because SB contributes to overcoming the limitations of GMOs. SB has been creating many tools and approaches for innovating conventional genetic engineering, for example, SB has been developing reliable biocontainment methods. Unfortunately, the draft implies that organisms created by SB would have a higher risk than non-GMO or classical GMOs. Overall, a clear definition and scope of SB should be provided in the revised draft. Based on a clear definition of SB, different subjects and methods under the umbrella of SB in the current draft should be reorganized by removing and adding them."	Changes made throughout document to indicate that synthetic biology is a multi-disciplinary area of research. Further, until consensus is achieved concerning which techniques, processes or products will remain under the definition of genetic engineering and those that will now fall under synthetic biology, there will always be a divergence of views and opinions on this amongst the readers. The authors recognise therefore that a "blurring of the lines" between the 2 may occur at times, however it is not the place for this document to champion any particular distinction between them, but instead to be as inclusive of as many definitions as possible (see Section B. Scope and Methods).
Republic of Korea	0	0	"Synthetic Biology TS No. 82 update draft deals with and well explains the vast contents of synthetic biology, but the following technologies need to be considered with more details: High-throughput (e.g., Next Generation Sequencing), Bioinformatics (computational biology), and fluid dynamics. With regard to NGS, DNA synthesis and improvement are accompanied by the advances in DNA decoding technology. Also, Bioinformatics systemizes complex and vast amount of biological information, while enabling big data collection and AI applications. Finally, the control of Microfluid enables a single cell at the nanoscale to be controlled, which drives the development of synthetic biology. The need for a regulatory governance for the development of synthetic biology should be more emphasized. Chapter D addressed the potential impacts of synthetic biology, but the actual contents are mainly focusing on the ‘concerns’ of synthetic biology. It would be recommended to include more positive impacts of synthetic biology, such as industrial and economic	Revision made.

			influences through technological innovation by Gingko or Moderna company, development of new genetic resources and accumulation of rapid scientific knowledge through the projects of YG 2.0 or GP-write etc., and survival of organisms in the extreme environment or in the space like NASA's Cubes. "	
Malaysia	0	0	Actually throughout the document, it has to be decided whether acronym for Invasive Alien Species which is IAS is going to be used or not. Sometimes it is spelt out in full, sometimes IAS is used.	Revision made.
Turkmenistan	0	0	**General comments** The National Institute of Deserts, Flora and Fauna (NIDFF) of the Ministry of Agriculture and Environment Protection of Turkmenistan would like to thank the Convention Secretariat for fruitful work, in cooperation with the International Centre for Genetic Engineering and Biotechnology (ICGEB), on development a draft of the updated technical series N.82 on synthetic biology. Turkmenistan as the country where have not carried out investigations on synthetic biology as well as synthetic biology applications on its territory, would like to highlight great significance, necessity and value of information and knowledge sharing on synthetic biology-related issues, because for us the synthetic biology is more "new and emerging issue". The draft of the technical series N.82 keeps large information for understanding the genetic engineering technologies and synthetic biology organisms, necessity of the management risks posed by synthetic biology to biodiversity conservation and their impact on human health. The NIDFF as research institute with dedicated research on biodiversity conservation in arid region of Asia to maintain applying the precautionary approach to the field release of synthetic biology organisms for identifying its impact on the three objectives of the Biodiversity Convention and related objectives of the Cartagena Protocol on biosafety and the Nagoya Protocol. In the XX century in the territory of Turkmenistan were conducted fundamental investigations on the feral-herd infections as malaria and local fauna of malaria mosquitos (*Anopheles maculipennis, An. superpictus, An. hyrcanus*). As we know, at present time engineered mosquitos (*Anopheles albimanus, Anopheles stephensi*) have been developed for the control of	Comments noted.

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

South Africa	0	0	As highlighted in the document, there are numerous typos that need to be fixed, these will not be mentioned further as requested.	Comment noted and revision made.
South Africa	0	0	After reading the entire document in detail, it was apparent that there was a notable amount of repetition between sections, either when examples were highlighted or when specific content from Conventions and Protocols were mentioned. It is understandable that there will be some degree of repetition which will be unavoidable but this could potentially be minimised by re-organising the flow of some of the sections. This would also make the document less dense and more reader-friendly.	Comment noted
South Africa	0	0	Throughout the document, it is emphasised that there is a need to engage with local people (indigenous or otherwise) in order to highlight concerns for new synthetic biology technologies and to gauge their acceptance for implementation of developed technologies. This was highlighted by Trump et al. (2020 – this reference was cited in the document for other reasons) who noted that an essential component for acceptance of synthetic biology technologies will have to involve co-operation between biosecurity experts, social scientists and practitioners. These authors termed this the "building of bridges" between the role players early in the technology development and forecasting stages. These authors demonstrated in another study (Trump et al. 2019), what they termed the value of the co-evolution of physical and social sciences in the development of synthetic biology over a 16 year period. It is recommended that this aspect needs to be expanded upon in the document as it is mentioned in very general terms.	Revision made.
South Africa	0	0	While reviewing the literature on regulation of synthetic biology under the CBD, an interesting review article by Keiper and Atanassova (2020) was noted (this was cited numerous times in the document). These authors concluded that the CBD discussions on synthetic biology were seen as a longer version of the Asilomar conference as the decision making process has been in progress for an extended period of time. These authors also highlighted the general lack of participation of practitioners in the CBD decision making process. The authors further advocated for more active involvement by the scientific community in order to drive efficient, science-based regulation.	Comment noted and revision made.

South Africa	0	0	It is recommended that more emphasis be placed on international co-operation in terms of regulation and implementation of new technologies, for example, gene drives which have the potential for transboundary movement. This is highlighted by Reynolds (2020 – cited in the document) in terms of international governance of gene drives.	Comment noted.
South Africa	0	0	The document is very comprehensive and seeks to provide useful information on synthetic biology as it relates to the Convention and its Protocols. However, most sections seem to be repeating information from the text of the Convention and its Protocol, mostly as background and to provide context, but in some cases seem irrelevant or lack a link to synthetic biology. We propose that background information be reduced and only keep as far as possible shorter paragraphs that provide context to the aspects of synthetic biology discussed in the different sections.	Comment noted and revisions made.
South Africa	0	0	A significant challenge to resolving CBD guidance and advice on Synthetic biology is the current 'operational definition' of Synthetic biology which states: "Synthetic biology is a further development and new dimension of modern biotechnology that combines science, technology and engineering to facilitate and accelerate the understanding, design, redesign, manufacture and/or modification of genetic materials, living organisms and biological systems". This is a very broad definition, which potentially covers all aspects of genetic engineering ranging from genetic modification (already well considered under the Cartagena Protocol on Biosafety) through to the de novo creation of synthetic life (hereafter termed novel life). The definition therefore prevents Synthetic Biology being a useful term for defining regulatory scope, as it covers large parts which are already defined and extensively dealt with under the CPB (including, potential future modification technologies), but also areas that will need new considerations, and will require different approaches (from genetic modification) to risk assessment and risk mitigation. This then causes confusion when the question is asked (such as during the recent SBSTTA) whether Synthetic Biology is a "New and Emerging Issue", as – on the one hand - genetic modification is well covered, and therefore clearly not a new and emerging issue, while other aspects of Synthetic biology are indeed	Until consensus is achieved concerning which techniques, processes or products will remain under the definition of genetic engineering and those that will now fall under synthetic biology, there will always be a divergence of views and opinions on this amongst the readers. The authors recognise therefore that a "blurring of the lines" between the 2 may occur at times, however it is not the place for this document to champion any particular distinction between them (see Section B. Scope and Methods).

			new and emerging, - as per the criteria provided in Decision IX/29. There are two possible solutions. Firstly, it would be to redefine Synthetic Biology as "A new dimension of modern biotechnology that combines science, technology and engineering with the objective of creating life/living organisms with limited or no resemblance to existing or extinct organisms". This would then clearly differentiate Synthetic Biology from genetic modification (which generally has substantial equivalence to existing, unmodified organisms), and allow the CBD to proceed with new considerations beyond living modified organisms (i.e. Novel life), for which there is no existing comparator organism. There are two possible solutions. Firstly, it would be to redefine Synthetic Biology as "A new dimension of modern biotechnology that combines science, technology and engineering with the objective of creating life/living organisms with limited or no resemblance to existing or extinct organisms". This would then clearly differentiate Synthetic Biology from genetic modification (which generally has substantial equivalence to existing, unmodified organisms), and allow the CBD to proceed with new considerations beyond living modified organisms (i.e. Novel life), for which there is no existing comparator organism. The availability of a relevant comparator is a critical distinguishing issue, as it forms the basis for the existing risk assessment process as defined under the CPB. The modified organism is compared with the existing organism, taking into account the modification. A novel organism has no directly equivalent comparator, and therefore the risk assessment process is necessarily different. The alternative solution – albeit eroding its functional utility - is to retain the term Synthetic biology as an all-encompassing term, but recognize that is includes two substantial sub-classes – living modified organisms, and novel organisms. The distinction would be whether there is substantial equivalence to an existing organism (which would form the basis for deciding what risk assessment approach can be used). Synthetic biology could then not be identified as a 'new and emerging issue', but the novel category (or sub categories of these) could be. It further needs to be recognised that issues like Genome editing and Gene drives are genetic engineering techniques that could be applied either to modifying LMOs, or to novel organisms, and the risk assessment process	

			for either category (although not yet developed for novel organisms) would still hold.	
Brazil	0	0	Although this document is part of a Technical series, thus is should be focusing on a technical and scientific compilation of information, it presents a lot of “opinions” and speculative sentences in the executive summary and key messages that are not suitable for the goal of the document. In addition, the document does not mention in any part Article 19 of CBD (handling of biotechnology and distribution of its benefits) and mentions very briefly the third CBD objective (fair and equitable sharing of benefits from access to genetic resources). All the suggestions below were made to present a more balanced view, which has already been expressed during the SBSTTA-24 discussions and should be reflected in the text. An additional suggestion would be to include a section about “The concentration of R&D of synthetic biology in developed countries and the exploitation of possible mechanisms to promote the access of developing countries to biotechnological research and its benefits to face the global challenges”. The suggestions of inclusion are in bold text, and the strikethrough text should be excluded.	Comment noted. Revision made.
Argentina	0	0	General comments on the document: We consider that given that there is no agreed definition of synthetic biology, the draft describes all biotechnological developments, rather than synthetic biology applications. We disagree with the inclusion of several of the applications that are presented as synthetic biology in this document. In particular, we consider that genome editing does not qualify as synthetic biology. This document includes genome editing and describes an example containing a point mutation, a change that could be achieved using conventional breeding. In this regard, this case should not be considered as something completely new that deserves a new approach or particular consideration. We consider that examples including applications of genome editing resulting in changes comparable to those achieved by conventional methods should be excluded from this document.	Until consensus is achieved concerning which techniques, processes or products will remain under the definition of genetic engineering and those that will now fall under synthetic biology, there will always be a divergence of views and opinions on this amongst the readers. The authors recognise therefore that a "blurring of the lines" between the 2 may occur at times, however it is not the place for this document to champion any particular distinction between them. (see Section B. Scope and Methods).

New Zealand	0	0	We note that there is a great deal of discussion in the document devoted to issues that we would not consider "technical", such as dual-use applications and ethical and moral issues. It would be our preference that a technical document such as this one avoid discussion on issues of a more political nature. This is exemplified by the fact of numerous decisions under the Convention regarding these matters generally are qualified by the phrase "according to national circumstances", or similar language.	Comment noted. See scope and methods.
New Zealand	0	0	We note that the authors stated that the examination of Synthetic Biology was taken to encompass a very wide range of technologies and applications. They additionally stated that not all readers would have the view that many of the technologies and applications are in fact synthetic biology. Given these caveats, we think that calling synthetic biology a "discipline" is something of an overreach.	Revision made.
New Zealand	0	0	Additionally, given the "broad brush" approach taken by the authors as to what actually constitutes synthetic biology, many (if not most) of the applications discussed appear to be for the simple development of LMOs, which do not require any special treatment under the Convention beyond the procedures already established under the Cartagena Protocol for Biosafety. Similarly, CAR T-cells, cultured meat, genetic rescue and de-extinction research and applications do not constitute synthetic biology. We are concerned that examination of such research will lead to duplication of effort regarding technologies and research that can be adequately covered under either the Cartagena Protocol, or other international agreements on (potentially) hazardous substances. Such resources would be put to better use in efforts to actually conserve biological diversity.	Until consensus is achieved concerning which techniques, processes or products will remain under the definition of genetic engineering and those that will now fall under synthetic biology, there will always be a divergence of views and opinions on this amongst the readers. The authors recognize therefore that a "blurring of the lines" between the 2 may occur at times, however it is not the place for this document to champion any particular distinction between them (see Section B. Scope and Methods).
New Zealand	0	0	Furthermore, many of the applications discussed involve the synthesis of biological molecules, eg, DNA and RNA. We think that the simple synthesis of biological molecules (and their downstream applications thereof, such as cell-free systems) is not synthetic biology. In fact, the discussion on many of the applications under discussion tend to echo the assessment of LMOs, in that the product of a "modern biotechnology" process (eg, vanillin) is somehow viewed to be different to vanillin	See scope and methods. The document is based on the operational definition of synthetic biology, considered as a useful starting point for discussions by the COP.

			produced via organic chemistry processes, or purification from natural sources, despite no differences in the actual molecules so produced or derived. Therefore, chemical products that result from any application of synthetic biology (eg, vanillin, RNA, DNA, etc.) are in fact not covered under the CBD, and there are existing international treaties that cover any potential adverse effects that they may have on the environment as substances. This document should therefore restrict itself to organisms so as to avoid duplicative processes among multiple international agreements.	
New Zealand	0	0	The discussion of developers of "synthetic biology" to publish and discuss concepts and applications prior to the initiation of any work is problematic, because it does not take into account the scientific method or process. Concepts are very rarely realised in full because research and experimentation reveal limitations of the concept, or improvements relative to the initial concepts. Concerns regarding dual-use applications being used as a reason to limit lines of scientific enquiry does not take into account that only those willing to act in good faith would be bound by such restrictions. Openness regarding such research also allows concomitant lines of research on the prevention or mitigation of the effects of dual use applications of a technology, leading to better outcomes than suppression of independent lines of thought. Risk assessment and risk management methodologies would apply to the containment of such organisms and/or substances.	Comment noted
New Zealand	0	0	Finally, despite the clear discussion of the potential environmental benefits in the main text of the document, the Executive Summary and Key Points appear to be rather skewed toward the discussion of risks and potential negative outcomes from synthetic biology. We do not think that this is reflective of the potential applications of Synthetic Biology and their concomitant benefits, and it would be helpful to see these sections of the document more accurately reflect the discussion in the main body of the text.	Comment noted. Revision made.
European Union	0	0	"General comments that are applicable to the entire report: - Only a fraction of relevant publications are cited throughout the report – many more relevant papers (including more recent ones) have been published in the scientific literature and would be worthwhile citing;	Comments noted and revisions made.

			- It may be helpful to clarify the criteria used for selecting, citing or excluding relevant publications; - A narrative approach is followed to describe some of the relevant information reported in the scientific literature. Yet, the weight of evidence given to the publications cited and statements made therein is not reported, suggesting that each single scientific publication has been attributed an equal weight. However, the quality of scientific publications cited can vary; - For transparency it would be helpful to "quote" the sentences reused/copy pasted from scientific publications; - In several cases, a single reference is cited to substantiate a statement made in the report, though other publications could be cited in support of that statement; - Several general statements are made throughout the report, without specifying whether these statements are applicable to all potential SynBio applications or specific ones only. This is confusing, as in many cases, the statements made should not be generalised. It would therefore be helpful to remain as specific as possible and follow a case-specific approach in the report; - Several of the general statements made are not specific to SynBio applications; - To focus the report further, perhaps it may be helpful to single out the novel features of SynBio applications as compared with "contemporary" GMOs, "	
Ecuador	0	0	The ambiguous definition for "synthetic biology" adopted in the document does not allow a correct interpretation of the context of this technology as a multidisciplinary field of study, in addition to showing in the document some examples that are not necessarily considered as products derived from SynBio. On the other hand, an unbalanced analysis is made between the potential negative impacts derived from the use of the technology to the detriment of its potential benefits.	Revision made.
Ecuador	0	0	We consider necessary to highlight the importance of maintaining solid technical-scientific criteria when assessing potential risks derived from the use of this technology that may threaten the objects of protection established as a state, and we also recognize the importance of the	Comment noted. Revisions made.

			participation of the different actors that would allow the strengthening of a diverse and science-based analysis.	
Ecuador	0	0	Regarding genetic resources, it is important to take into account the current benefit sharing instruments specially the Nagoya Protocol that embrace the DSI approach related to synthetic biology	Comment noted.
Ecuador	0	0	It is recommended to invite and promote alliances with private sector, academics and other stakeholders in order to increase the capacity building, scientific researches and technology transfer related to synthetic biology	Comment noted.
Malaysia	0	48	Under the sub-title 5.1, Societal Concern, the technical dossier touches on (1) Incorporating societal concerns into regulatory decision-making and (2) Indigenous Peoples and Local Communities (IPLCs); however there is no input on Synthetic Biology Education (SBE) in the technical dossier. The element was also missing the Sub-Topic 8.2.3 (page 92) and Topic 10 (page 128). It is well described in the dossier that the Synthetic Biology will become economic, social and politically important in the near future. Therefore, I think it is up most important that the element of SBE should be included in the dossier as such the agendas enable stakeholders (eg.student) learn to achieve predictable, measurable learning outcomes and build a framework on the SBE subject.	Comment noted.
Malaysia	0	92	Sub – topic 8.2.3 report on Other relevant provisions of the Protocol such as capacity building and public awareness and participation.	Comment noted. See Sections 8.1.6 and 8.2.3(d)
Malaysia	0	128	10. Challenges, Gaps and/or Overlaps associated with synthetic biology governance.	Comment noted
South Africa	03	06	OPCW full description not provided	Revision made.
Argentina	08-15		General comments on the executive summary: It should reflect that “synthetic biology” has not been defined yet. We disagree with the statements about the existence of gaps in the current regulation and in the use and impact of the technologies. It is not clear why the draft includes genome editing applications. These applications are not considered LMOs in many countries.	Revision made. See scope and methods.
Republic of Korea	08	01-48	Should mention the benefits of synthetic biology for diversity	Revisions made.
Thailand	08	02-05	The provided definition of synthetic biology is pretty broad. While there is still no single definition of this field, it might be useful to add some	Comment noted. See scope and methods for clarity on the scope and definition.

			clarification regarding the differences between synthetic biology, genetic engineering and biotechnology (if there is any).	
Brazil	08	06	"As the discipline continues to advance rapidly and expand beyond the confines of the laboratory, ~~the potential of~~ synthetic biology ~~carries hopes and aspirations~~ **presents potential solutions** to address a multitude of global challenges related to food, health and the environment, among others, but also concerns about potential risks including those associated to biodiversity".	Revision made.
United States of America	08	09	"We suggest clarifying the text below to indicate whether there are synthetic biology techniques that are not ever used in applications of genetic engineering. If so, request that these techniques be included here or later sections. "Synthetic biology relies on a suite of supporting technologies and tools, some of which are also used in genetic engineering.""	Comment noted and revisions made.
South Africa	08	10	We propose that the word "sector" be qualified. As it currently stands, it is not clear which sector is being referred to.	Revision made
Argentina	08	10-12	This statement is exaggerated and focused on genome editing, We propose to replace this sentence "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…" with: "The emergence of increasingly sophisticated technologies and tools has greatly expanded the potential range of applications and facilitated advances in plant and animal engineering, personalised medicine, and clinical therapeutics " We think the original phrases is misleading and it is not necessary to focus on genome editing.	Revision made
Brazil	08	12	"As a consequence, the number of applications, especially those that make use of genome editing technology, **although not all applications of genome editing fall under synthetic biology,** has increased exponentially and has led to advances in plant and animal engineering, personalised medicine, and clinical therapeutics".	Comment noted and revisions made

United States of America	08	13-15	Suggested text edits in red below. CRISPR is one technique in the suite of genome editing tools and we consider that it does not need to be specifically highlighted. Genome editing is used to introduce traits into agricultural products, which is separate and distinct from the technology itself. "Particularly, genome editing tools can be used to~~CRISPR-Cas technology is having~~ impact~~s in~~ agriculture, especially by introducing traits that increase~~ing~~ plant yield, quality, disease resistance and herbicide resistance, breeding, and accelerated domestication."	Comment noted and revision made
Argentina	08	13-15	"Particularly, CRISPR-Cas technology is having impacts" We do not agree to mention one particular tool. Besides, we believe that is too early to state the whether or not there are impacts.	Comment noted and revision made
Brazil	08	16	"Moreover, technologies such as engineered gene drives can now potentially be applied to a wide variety of organisms**, most of them are still in the research phase,** as a tool to spread **desirable** traits throughout a population".	Partial revision made
Republic of Korea	08	17-19	This three-way categorization of synthetic biology applications is useful from the perspective of researchers and industrialists, but it still needs to be further refined. For example, what does it mean by "contained"? Does it mean "managed"? Or "manageable"? Then, does "unmanaged" or "semi-manged" mean "uncontained"? Also, it is questionable whether the distinction between urban/rural settings is necessary here. (Consider also the part on page 29, line 11 and thereafter)	Comment noted. See section 3 for further clarification
European Union	08	19	Could you perhaps be more specific about "(i) contained, industrial, or laboratory settings, (ii) semi-managed, managed, or urban settings, or (iii) unmanaged or wild settings" by providing a short description/explanation in between brackets?	Comment noted. See section 3
Argentina	08	21	Synthetic biology is not a single discipline.	Revision made.

Brazil	08	22	"Although synthetic biology is often referred to as a single discipline, the numerous areas of synthetic biology research represent a wide array of potential **positive and negative** impacts, some of which are complex in nature and as a result, there is ~~a continuing need to acquire further data and knowledge~~ **need to use the experience with risks assessment and risk management of LMOs, to proceed with a stepwise approach, whereupon data and knowledge collected from experimental phases can inform the next stages of research,** to support the discussions about potential impacts".	Revision made.
Brazil	08	24-28	It is not appropriate to affirm that are methodologies or risk assessment science-based that can measure the impact of synthetic biology on socio-economic, moral and ethical aspects. ~~"The use of synthetic biology triggers a wide variety of views related to risks and benefits, moral and ethical values, along with broader issues such as socio-economic aspects. Therefore, a science-based assessment of any potential impact is seen as part of a wider decision-making activity; one that evaluates such economic, political, moral, and ethical concerns alongside a scientific analysis of the expected or potential changes that would result from using technology".~~	Revisions made.
South Africa	08	24-27	"It is proposed that the document maintains consistency when referring to the broader issues other than the scientific assessments, that is socio-economic, political, moral, cultural, legal, and ethical, ethical, socio-cultural, epidemiological, ecological and economic considerations social justice consistent with the Convention language? While acknowledging that these broader dimensions will vary depending on national circumstances, it would be useful to have these dimensions defined or expanded on in the context of synthetic biology."	Revisions made.
Brazil	08	30	"It is also important to stress that due to the diverse nature of the potential impacts, they cannot be generalised for all synthetic biology applications, and they should, by necessity, be considered on a case-by-case basis**, the same principle that is applied to risk assessment of LMO**".	Comment noted.
Brazil	08	31-33	"In this light, as synthetic biology applications approach commercial ~~deployment~~ **release** ~~and potential environmental release~~, this is bringing	Revision made.

			challenges to building consensus on how they are to be regulated, either under the same regimes as ~~classical genetic engineering~~ **modern biotechnology** ~~albeit with adaptations, or under new regimes yet to emerge~~ **with the necessary adaptations based on existing risk assessment frameworks and experience with risk analysis of different genetically modified organisms along decades**".	
South Africa	08	32-33	We proposed that the term "classical genetic engineering" be defined in a footnote	Revision made.
Argentina	08	32-33	"classical genetic engineering" is not defined yet.	Revision made.
Republic of Korea	08	38-	Fragmented landscape at the international level – This is an important issue to be addressed. I am glad that the report has pointed that out.	Comment noted.
Brazil	08	42-47	It is not appropriate to affirm that are methodologies or risk assessment science-based that can measure the impact of synthetic biology on socio-economic, moral and ethical aspects. ~~"Calls for improved governance of synthetic biology, including addressing gaps in the international legal and regulatory frameworks, place significant emphasis on the need to better address challenges that go beyond the scientific areas, and call to also consider societal, economic, and ethical dimensions. Enhanced regulatory oversight addressing these dimensions appears desirable to promote public trust and acceptance, however, the international laws, processes and initiatives analysed appear ill-equipped to address several of these dimensions".~~	Revisions made.
United States of America	10-11 (actually 8)	45-2	We do not believe that the assertion that "international laws, processes and initiatives" are ill-equipped is factual and we recommend that this part of the sentence be deleted: "~~Enhanced regulatory oversight~~ Further discussion addressing these dimensions ~~appears~~ may be desirable to promote public trust and acceptance~~, however, the international laws, processes and initiatives analysed appear ill-equipped to address several of these dimensions~~. With over a decade of substantive decision- making addressing synthetic biology, the Convention on Biological Diversity has emerged as an important international forum currently deliberating the potential impacts of synthetic biology ~~and its regulation~~, particularly as they relate to biodiversity and biosafety. The Cartagena Protocol on Biosafety provides the venue for	Revision made

			Parties to further discuss issues related to biosafety and potential socioeconomic considerations of products."	
Brazil	08-09	48, 1-2	"With over a decade of substantive decision making addressing synthetic biology, **including the decision about the criteria for synthetic biology to be considered a New and Emerging Issue under the agenda, and a topic that could not reach a consensus among Parties,** the Convention on Biological Diversity has emerged as an important international forum ~~currently deliberating~~ **for discussions about possible mechanisms to monitor and assess** the potential **positive and negative** impacts of synthetic biology and ~~its regulation~~, ~~particularly~~ as they relate to biodiversity and biosafety".	Revision made.
Brazil	09	03-11	It is not appropriate to expand the focus of governance beyond human health and the environment to a more holistic approach. The risk assessment must be science-based according to SPS Agreement. ~~"There is a recognised need to first better integrate and coordinate governance of synthetic biology, and secondly, to expand the focus of governance beyond the focus on biosafety, human health and the environment to a more holistic approach that also encompasses social impact, ethical principles, and elements of social justice, in accordance with national circumstances. To avoid unintended irreversible environmental damage and associated geopolitical challenges, innovative research guidelines, governance methods, integration with social sciences, and engagement with communities are needed. As we think about advancing synthetic biology into the future, the challenge is integrating the scientific freedom that allows research and product development to move ahead while acting responsibly and in a manner that embraces ethical, legal, and larger societal values".~~	Comment noted.
European Union	09	04	Delete "the focus on".	Editorial suggestions noted and revisions made.
Brazil	09	04-06	"There is a recognised need to first better integrate and coordinate governance of synthetic biology, and secondly~~, to expand the focus of governance beyond the focus on biosafety, human health and the environment to a more holistic approach that also encompasses social~~	Comment noted.

			~~impact, ethical principles, and elements of social justice~~ **to provide for the effective participation of developing countries in biotechnological research, as they provide the genetic resources for such research and to the results and benefits arising from biotechnologies** ~~in accordance with national circumstances~~."	
Republic of Korea	09	08-	"integrating the scientific freedom . . ." with what? This sentence looks incomplete. At the same time, the juxtaposition of scientific freedom and responsible research can give an illusive getaway without a wide-ranging discussion of what constitutes responsible research how to achieve it. We have to be reminded of somewhat disappointing inputs from the Human Genome Project's ELSI initiatives.	Comment noted.
European Union	09	23	Replace "issue" with "relevant applications".	Revision made
Argentina	09	27	("… whether and how..."), the text suggests that some products are not regulated, which is not true. All developments are regulated under particular regulations (for seeds, chemicals, etc.)	Revision made
Brazil	09	29	"The current debate also echoes similar views expressed at the emergence of ~~classical genetic engineering~~ **modern biotechnology** where developments were considered inherently risky by some, or not presenting any unique or novel risks by others".	Revision made
Brazil	09	31-33	"~~If discussions to date are anything to go by, those likely to fall under regulation will be subject to a thorough analysis of their different potential impacts on biodiversity-related issues as well as cultural, social, ethical and economic considerations~~ **The deliberation from synthetic biology AHTEG to date considers that all the synthetic biology organisms can be considered to be LMOs and that the risk assessment methodology according with Annex III of the Cartagena Protocol are adequate to assess those organisms**".	Comment noted.
United States of America	**11** (actually page 9)	**34-35**	We consider that this sentence is alarmist and factually incorrect since no technology is boundless. As a result, we recommend deletion or significant revisions to improve the tone and accuracy of the statement. "The potential of the synthetic biology toolbox is boundless, and so are the	Revisions made.

			opportunities for synthetic biology to have an impact in an unprecedented manner.”	
Argentina	09	34-35	"“have an impact in an unprecedented manner” “…the potential of synthetic biology toolbox is bondless…” These phrases are speculative and do not properly describe the situation of many countries address technologies with robust regulatory frameworks in order to guarantee biosafety."	Revision made
Republic of Korea	09	34-49	An insufficient balance between risk and benefit of synthetic biology	Comment noted. Revision made.
Brazil	09	35	“The potential of the synthetic biology toolbox is boundless, and so are the opportunities for synthetic biology to have ~~an impact in an unprecedented manner~~ **positive and negative impacts**”.	Revision made
Canada	09	40	The word “off” should be added following the word “pressure” to fully realize the meaning of the sentence.	Editorial suggestions noted and revisions made.
Thailand	09	40	… to take pressure “off” of wild populations,…	Editorial suggestions noted and revisions made.
New Zealand	09	40	“of” should be “off”	Editorial suggestions noted and revisions made.
European Union	09	47	Delete "such as" (written twice)	Editorial suggestions noted and revisions made.
Brazil	09	49	“These are only some of the many examples of synthetic biology applications that are having and could have ~~an impact in an unprecedented manner~~ **positive and negative impacts**”.	Revision made
European Union	09	43-46	Engineered gene drive applications are also under development to help rescue endangered species. Perhaps this additional type of application could be added to the list	Revision made
Thailand	10	04-05	Given a vague definition of synthetic biology, the ranges of estimated synbio market values and growth rates vary widely depending on reference sources. The authors should provide more detail on where these numbers come from.	Comment noted
Argentina	10	06	Products “produced in containment e.g. synthetic DNA, synthetic RNA, and oligonucleotides across various industries” are not considered as "synthetic biology".	Comment noted

Republic of Korea	10	10-	The expression, "essentially ubiquitous," looks too strong and deterministic. It has to be toned down and made humble.	Revision made
United States of America	10	15-16	We recommend including citations for this statement: "Moreover, technologies such as engineered gene drives can now potentially be applied to a wide variety of organisms as a tool to spread traits throughout a population."	Comment noted. Citations are not included in the Executive Summary
United States of America	10	19	We are not aware of a commercially viable engineered gene drive on the market to date. We recommend including a citation for the following statement or the following insertion: "Amongst each of these categories, several synthetic biology products are being commercialised, or are in a research and development stage."	Revision made.
Malaysia	12 (is actually p10)	20	The sentence might miss a specific word ie lagging behind??	Editorial suggestion noted and word inserted.
United States of America	10	25-28	We recommend that the following statement be edited and clarified. It is not clear to us who is meant when the text indicates "Seen". We note that evaluation of non-science based factors are not an obligation of the CBD or its protocols. "Therefore, a science-based assessment of any potential impact is seen by some Parties as part of a wider decision-making activity; ~~one that~~ some Parties may be interested in considering ~~evaluates such~~ economic, political, moral, and ethical concerns ~~alongside a scientific analysis~~ of the expected or potential changes that would result from using technology. Such considerations should be conducted in a manner that is consistent with other international obligations."	Revision made
United States of America	10	31-32	We recommend the following edit: " this is bringing opportunities and challenges to building consensus on how they are to be ~~regulated~~ considered"	Editorial suggestion noted.
Malaysia	10	32/33	The phrase…"and the EU each one, is not very clear. Is it is meant to be one funder was identified from each of the EU member state? A rewording is suggested here.	Revision made

			Suggestion would be….the UK, and one from South Korea and each of the EU Member state.	
Malaysia	10	33/34	This statement that starts with "The great majority of funders…" lacks clarity. Suggestion would be…The top 50 funders are mainly from public research councils or government agencies	Revision made
United States of America	10	33-35	We recommend the following edit, to reflect that many countries are using approaches other than "regulation" to address these products: "At a national and regional levels, ~~regulatory~~ policy frameworks are developing at different rates and with differing perspectives with respect to synthetic biology governance."	Revision made.
Brazil	10	34	Include in the end of the paragraph: "**Those numbers of publications reflect how research and development are concentrated on developed countries and the urgent necessity to democratize the access to technology as a global solution for the environmental crisis**".	Comment noted.
European Union	10	37-39	In this section, more emphasis could be put on the intended uses of SynBio organisms and their intended outcomes, as these aspects will be key for the identification of plausible pathways to potential harm (idem for section 7 on page 11)	Revision made.
United States of America	10 [actually 8]	38	We are not clear what the use of the word "laws" in the following phrase is intended to capture and we recommend the following edit to enhance the clarity: "Currently, the governance of synthetic biology is supported by a range of international ~~laws~~ obligations, processes, and initiatives,	Comment noted.
New Zealand	10	43	"organism" should be "organisms"	Editorial suggestions noted and revisions made.
Brazil	10	44	"Currently, of those synthetic biology products that are **already submitted to a risk assessment and** commercially available and intended for use in semi-managed, managed, or urban settings, there are two genome edited	Comment noted

			crops, self-limiting insects, and biological nitrogen fertiliser based on engineered bacteria".	
Argentina	10	44-45	Genome editing crops and self-limiting insects are not examples of synthetic biology.	Comment noted see clarifications on Scope and Methods.
Canada	10	45	Missing period following "bacteria".	Editorial suggestions noted and revisions made.
New Zealand	10	45	Full stop (period) at end of line needed	Editorial suggestions noted and revisions made.
United States of America	10	46	We recommend inclusion of references to support the statement below both here and when mentioned elsewhere in the document. At present, we know of no gene- drive modified organisms that are in the pipeline and could reach the market in the next few years. "It is expected that some other genome edited organisms and potentially those containing engineered gene drives could reach the market in a few years."	Revisions made.
Brazil	10	46	"It is expected that some other ~~genome edited organisms and potentially those containing engineered gene drives~~ **synthetic biology organisms synthesized with genome editing or containing engineered gene drive** could reach the market in a few years".	Comment noted.
European Union	10	47	The terminology "… reach the market" may not be the most appropriate one to use for engineered gene drive applications, as some of these applications may include public or non-commercial use (e.g. philanthropic/charitable purposes). Perhaps alternative wording may be needed for clarity	Revision made
European Union	10	47	The terminology "in a few years" is a bit vague. Can this be made more specific?	Revision made
Brazil	11	01	"~~As only a few synthetic biology applications developed for direct use in the environment have been commercialised, relatively little "real world" data has been collected concerning their potential impacts~~ **Only a few synthetic biology applications developed for direct use in the environment have been commercialized and the risk assessment framework for LMOs is being used**".	Editorial suggestion noted and text revised.

European Union	11	01-10	The statements made in section 7 are very general, and may need refinement on a case-by-case basis	Text revised.
Malaysia	11	02	"What is meant by "real world" data is not clear. Perhaps to explicitly describe what is meant by "real world" data. Data obtained from actual environmental release."	Revision made.
United States of America	11	03-10	We recommend inclusion of the text insertion below in red: Thus, the discussions on potential impacts have been informed mostly by previous experience with LMOs and associated benefits and concerns.	Editorial suggestion noted and text revised.
Brazil	11	05-06	"The range of potential impacts of synthetic biology applications on the conservation and sustainable use of biodiversity ~~remains largely hypothetical/speculative due to~~ **is being assessed using the experience and methodology used for LMOs as those synthetic biology organisms are considered to be LMOs, although** the limited number of commercial ~~products~~ **organisms** developed specifically for use in the environment that are currently available".	Comment noted. Revision made.
Brazil	11	08	"Thus, the discussions on potential impacts have been informed mostly by previous experience with LMOs ~~and associated concerns~~".	Editorial suggestion noted and revision made.
Brazil	11	08-10	"~~This is bringing challenges to arriving at consensus on whether synthetic biology applications are to be assessed, and regulated under the same regime, which itself is beginning to adapt to these applications~~ **There still a speculative view about the challenges for future synthetic biology organisms applications and whether adaptations or reformulations to the current risk assessment frameworks will be necessary**".	Editorial suggestion noted. The text of the message has been revised.
Brazil	11	11-13	"~~Many of the impacts that were originally expected were overly simplistic in nature, with latest experience demonstrating that the situation is far more nuanced and with multiple factors adding to the complexity~~ **There are multiple factors to be considered, both positive and negative, for decision-making about synthetic biology applications**".	Editorial suggestion noted. The text of the message has been revised.
European Union	11	11-26	"A few cases are presented and used to make generalisations for all potential SynBio applications, which may not necessarily be applicable to	Comment noted. Revisions made. Also, please see clarifications on scope and methods.

			all such cases in practice. It may be helpful to avoid making generalisations based on a few case studies only. In addition, it is worth noting that most of the considerations in this section are not specific for SynBio."	
Argentina	11	14-15	The text suggests that products of synthetic biology "could also disrupt in situ conservation projects" – What is the evidence about this?	Revision made.
Saint Lucia	11	17-18	Why have illegal in brackets	Revision made.
Canada	11	20	The word "topical" is likely meant to say "tropical".	Editorial suggestions noted and revisions made.
New Zealand	11	20	"tropical", not "topical"	Editorial suggestions noted and revisions made.
Brazil	11	24-26	"This complex web of potential interactions derived from the use of synthetic biology applications in various scenarios is therefore adding to the challenges ~~of assessing the potential impacts that could be associated with their use~~ **of decision-making about synthetic biology applications**".	Comment noted. Text of message has been revised.
Brazil	11	30-32	"~~Recognising the global nature of synthetic biology applications and the fact that local communities are most likely to be impacted first, it would be advantageous to communicate concepts of new applications prior to large investments of time and resources (e.g. construction, testing and release)~~".	Text revised.
European Union	11	30-31	The statement that "local communities are most likely to be impacted first" is a generalisation that does not apply to all cases, since the impacts and impacted stakeholders will depend on the specific application. We suggest to replace with "local communities may be those to be impacted first".	Text revised.
Malaysia	11	33	"IPLC is not expanded, however it is mentioned again in pg 12 Line 6 and pg 16 Line 12, where by its full meaning is expanded"	Editorial suggestions noted and revision made.
Brazil	11	39	"Further, since most research and development of synthetic biology applications occurs in relatively few countries, outreach and engagement with intended recipient communities will be important when considering ~~deployment~~ **release** in other geographical locations, especially as there may be a need for further 39 building of local regulatory capabilities".	Editorial suggestions noted and revisions made.
European Union	11	42-43	"It would be helpful to clarify better whether such an engagement is needed for all SynBio applications or specific applications only.	Comment noted. Revisions made.

			Moreover, the need for such engagement should be better explained, and be put in the context of contemporary GMOs (in terms of lessons learnt)"	
Brazil	11	44-48	"Regulatory decision-making on activities involving synthetic biology products ~~requires more than just a crucially important assessment of characterised risks and potential prescribed risk management strategies, as the degree to which a risk is acceptable is a social construct, as are the guiding policy goals. Neither can be determined purely scientifically and should instead be informed through consultation with a broad set of stakeholders, including the populations likely to be impacted most~~ **maybe requires, according with national legislation and circumstances, consultations with a broad set of stakeholders, including the population likely to be impacted most, after a science-based risk assessment and management is conducted**".	Editorial suggestion noted.
United States of America	11	44-48	We have made suggested text edits in red below. As currently written, this statement implies that existing risk assessment and management strategies across the board are not fit for use and need to be revised. We consider that stakeholders must also be provided essential information as to the benefits of the associated products/applications. "Regulatory decision-making on activities involving synthetic biology products requires more than just a crucially important assessment of characterised risks, potential benefits, and potential prescribed risk management strategies, but should also include ~~as~~ the degree to which a risk is acceptable ~~is a social construct, as are the guiding policy goals. Neither can be determined purely scientifically and should instead be informed~~ through consultation with a broad set of stakeholders, including the populations likely to be impacted most."	Editorial suggestion noted.
Brazil	11	48-50	"~~For emerging technologies, especially synthetic biology, that affect the global commons, there has been a call for concepts and applications to be published in advance of construction, testing, and release~~".	Editorial suggestion noted. Revision made.
Canada	12	23	Appears to be an incomplete sentence.	Editorial suggestions noted and revisions made.
Malaysia	12	23	This statement seems to hang, it is not complete	Editorial suggestions noted and revisions made.
Thailand	12	23	Misplaced sentence	Editorial suggestions noted and revisions made.

South Africa	12	23	Incomplete sentence "of those countries form the basis of discussions aimed at reaching a consensus at the international level."	Editorial suggestions noted and revisions made.
Brazil	12	23	The sentence lacks the initial words.	Editorial suggestions noted and revisions made.
New Zealand	12	23	The entire line is a fragment, out of place with the rest of the paragraph	Editorial suggestions noted and revisions made.
European Union	12	23	Incomplete sentence	Editorial suggestions noted and revisions made.
Brazil	12	29-31	"~~Due to its interdisciplinary nature, s~~**S**ynthetic biology presents particular challenges for the regulatory system as applications of synthetic biology have the potential to accelerate the pace of technological development across multiple sectors, ~~with the promise of~~ **and** helping to solve some of humanities greatest challenges this century".	Editorial suggestions noted.
New Zealand	12	31	"humanities" should be "humanity's"	Editorial suggestions noted and revisions made.
Brazil	12	34-37	"Often, international and national regulatory regimes tend to focus on biosafety risks **as part of science-based risk assessment** ~~rather than a more holistic approach~~ **while a more holistic approach could be part of a decision-making** that takes into account a range of public interest issues related to the biosecurity, ethics, societal, cultural and economic implications of synthetic biology more broadly, as well as potential benefits related to biodiversity conservation and sustainable use **and also and the important benefits for human health and food security**".	Editorial suggestions noted and revisions made.
South Africa	12	34-38	While socio-economic considerations as outlined in Article 26 of the Biosafety Protocol are not mandatory, most Parties have specific approaches or requirements that facilitate how socio-economic considerations should be taken into account in decision-making with regard to living modified organisms. South Africa's NBF for example, has a holistic approach that considers both biosafety aspects and socio-economic consideration in decision-making. As such, organism resulting from synthetic biology techniques considered as LMOs would be accommodated.	Comment noted. Revision made.
Brazil	12	37-38	"~~In this sense, a new paradigm for regulating synthetic biology applications is needed that looks beyond just biosafety~~".	Comment noted and text revised.

Argentina	12	37-38	“In his sense, a new paradigm for regulating synthetic biology applications is needed”. We do not find evidence to justify that a new paradigm is needed.	Comment noted and text revised.
Canada	12	40-45	Health Canada has engaged in a number of regulatory foresight exercises in the past on synthetic biology, and biotechnology more broadly, involving information gathering on the latest research and development activities in these areas that are aiming at commercial application. This has allowed us to better determine how effectively our current regulatory systems can address any risks and whether changes in policy, regulation or regulatory capacity may be required. Suggest adding text here encouraging regulatory agencies to conduct such regulatory foresight exercises on a regular basis.	Comment noted. Revision made.
New Zealand	12	41	“cope-up” should be “keep up”	Revisions made.
United States of America	12	43	"We recommend the inclusion of more support for this statement here and elsewhere in the document. We also recommend that evidence be provided to support the supposition that nations will not be able to adequately assess products suggesting the creation of domestic or international mechanisms that consistently assess the field of potential products beyond what are currently in place, and this language could usefully be amended to enhance the clarity of the sentence. “Considering the fast pace of development of synthetic biology, and the challenge for regulatory regimes to cope with potential new applications, an early screening of what is under research and development and their commercialisation perspectives will be critical in providing timely information for countries and organisations to react and adapt if necessary.” "	Comment noted. Revision made.
Brazil	12	44	“Considering the fast pace of development of synthetic biology, and the challenge for regulatory regimes to cope with potential new applications, an early screening of what is under research and development and their commercialisation perspectives ~~will be critical~~ **should be considered due to the potential** in providing timely information for countries and organisations to react and adapt if necessary”.	Comment noted and text revised.

United States of America	12	47	We have made suggested text edits in red below. We consider that the rationale behind this statement is unclear. The adoption of the term "synthetic biology" after the establishment of regulatory process does not necessitate that those processes require updating. Our suggested edits reflect that new tools have come into use and that there are new *products/applications* that may require updated regulatory mechanisms to assess. "14. Manyost regulatory mechanisms were developed before some tools that enablethe term synthetic biology became widely used and these mechanisms may need updating to address some applications of synthetic biology."	Editorial suggestions noted and revisions made.
South Africa	12-13	49-50 and 1-2	"It would be useful to put into context "regulatory mechanisms/frameworks" referred to as at not having been developed with the necessary scope and scale, especially given that it is implied that there are others beyond the Convention and its Protocols. It would be useful to gather information on regulatory frameworks under which synbio applications have been considered by parties thus far to get an idea of the extent to which they accommodate synthetic biology. This can assist other parties in assessing the appropriateness of their regulatory frameworks and whether there would be a need to update based on national circumstances."	Text has been revised.
Argentina	13	04	What is a "conventional LMO"? The term is confusing. We can refer to LMO or modern biotechnology as a broad term that includes LMO and New Breeding Techniques, or even conventional (traditional) biotechnology to refer to past techniques, but we cannot speak of "conventional LMOs"	Revision made.
Brazil	13	05-07	"~~This will require a concerted effort from all stakeholders to adapt existing frameworks in order to "future-proof" them for synthetic biology applications~~".	Comment noted.
United States of America	**13** (actually page 11)	06-8	We recommend inclusion of the text insertion below in red: Thus, the discussions on potential impacts have been informed mostly by previous experience with LMOs and associated benefits and concerns.	Revision made.

United States of America	13	09-10	We suggest inclusion of the edits shown in red below. “International governance and regulation” may inaccurately imply that a single international body/coherent structure is currently in place or necessary for SynBio applications. Our recommended edits reflect that governance and regulatory bodies are supported at the national level. “~~Intern~~National governance, ~~and~~ regulation, and use of applications of ~~associated with~~ synthetic biology is complex and would benefit from a coordinated and cooperative approach.”	Key messages section has been revised.
Brazil	13	11	“Considering the broad scope of not only synthetic biology research, but also the ~~potential impacts~~ **positive and negative** of its products and applications, it is not surprising that no international treaty framework nor institutions exist with a sufficient mandate to regulate the full spectrum of possible synthetic biology activities or impacts”.	Editorial suggestions noted and revisions made.
United States of America	13	11-26	We consider that this entire paragraph is also alarmist and factually incorrect. We recommend the inclusion of citations and significant revision.	Key messages section has been revised.
European Union	13	13	Replace “impacts” with “products”. Activities and products are regulated, not impacts.	Editorial suggestions noted and revisions made.
Brazil	13	19-20	We agree that it is important to acknowledge the competencies of existing fora and have reflected this in the updated textwhich reads as follows: “As the primary forum deliberating the governance of synthetic biology applications and products in relation to potential impacts on biodiversity-related issues, the framework of the CBD provides unique opportunities for hosting discussions**, respecting the competencies of other international fora,** aimed at improving coordination and addressing challenges and cooperation opportunities **for effective participation of developing countries on biotechnological research,** which are apparent in the governance of synthetic biology without the need to invent/create another series of fora”. On the second issue, we do not consider it appropriate to limit cooperation opportunities, however, the proposed text has has been included a an example "for example, aimed at ensuring effective participation of developing countries on biotechnological research".	Revision made.

Brazil	13	25	“Therefore, aspects such as coordination, cooperation, capacity-building, knowledge-sharing**, technology transfer** and communication are of paramount importance”.	Editorial suggestions noted and revisions made.
Brazil	13	28	“The governance of synthetic biology cannot advance if the approach towards it is narrow or if it lacks the support of the various entities and stakeholders who play a key role in its development **dissemination**, potential regulation and potential use”.	Editorial suggestions noted and revisions made.
Argentina	13	33-34	""“there is a growing urgency to discuss the evolution of a more cohesive international regulatory environment” – there is no evidence to sustain this statement. Most countries already have regulatory systems capable of addressing synthetic biology."	Comment noted revision made.
Brazil	13	34	“This is further exacerbated by the large number of near-market applications, and as such, there is a growing urgency to discuss the evolution of a more cohesive international regulatory environment **and mechanisms for broader participation of developing countries on research and development of biotechnological solutions**”.	Key messages section has been revised.
Brazil	13	38	“Moreover, as synthetic biology will continue to grow in 34 relevance and importance due to the opportunities that it offers towards solving global challenges, it is 35 imperative that resources are available concurrently for research and development, and for the 36 development and or adaptation of regulatory systems that could provide the needed safety that should 37 accompany any potential use **and distribution of its benefits**”.	Comment noted.
South Africa	13	40	It is recommended that Table 1 be moved closer to where it is first cited (i.e. page 10) for ease of reference. Currently, there are a number of other sections that appear before Table 1.	Comment noted.
Malaysia	13	50	This is being practiced under the Malaysian National Biosafety Law especially on GMO, GED whereby notification is needed before any related work to GMO,GED is undertaken	Comment noted.

European Union	13	40 (table 1)	The terminology "commercially available" may not be the most appropriate one to use for engineered gene drive applications, as some of these applications may include public or non-commercial use (e.g. philanthropic/charitable purposes). Perhaps alternative wording may be needed for clarity It may be more helpful to present the table in the core text than in the summary of the report, or twice, both in the summary and core text. As stated in the text on page 15 lines 19-23, "the authors 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". Taking into account the definition of synthetic biology, the simple use of genome editing techniques does not make a product a synbio product. In the light of this definition, table 1 presents some applications whose classification under synthetic biology is not justified (e.g. general reference to "genome edited crop plants and farm animals", in the column on "advanced developments", and specific reference to "genome edited soya bean and oilseed rape" in the column on "commercially available" applications). We recommend to: 1) Replace "genome edited crop plants and farm animals" with "synbio applications of genome edited crop plants and farm animals". 2) Delete "genome edited soya bean and oilseed rape" from Table 1 and other sections of the document. 3) include the disclaimer above in Table 1 and also in other relevant parts of the document (e.g. page 31, section 3.2.)	See S&M section for clarification. A revision has been made. Disclaimers are now incorporated as footnotes.
United States of America	14	27-38	We believe that this section would benefit from the addition of a factual sentence, noting the cost and burden overly restrictive evaluation of products may have on the ability for synthetic biology to live up to its perceived potential. We recommend the addition of text along the following lines: "The regulation and evaluation of synthetic biology products should be conducted in a manner that is risk-proportionate. Science- and risk-based assessments can support the streamlined commercialization of safe products. The incorporation of other factors into decision making processes	comment noted.

			should be done in a manner that is consistent with international obligations and not at odds with the findings of a science-based risk assessment. Parties should strive to avoid inhibiting or slowing the commercialization of products that could contribute to the goals of the Convention and its protocols."	
Argentina	14	table	We request to remove the following applications from the table since they are not synthetic biology: - Transient modification of agricultural plants through RNAi spray or nanomaterials - 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	Until consensus is achieved concerning which techniques, processes or products will fall under synthetic biology, there will always be a divergence of views and opinions on this amongst the readers (see Section B. Scope and Methods).
Malaysia	14, 15	38, 16	Referring to: a new paradigm for regulating synthetic biology applications is needed that looks beyond just biosafety. For the Synthetic biology regulation and governance; consensus and alignment are needed between all parties involved ie biodiversity, biosafety, biosecurity, health, FPIC etc etc	Comment noted. Revision made
Brazil	15	11	Perhaps include other definitions of Synthetic Biology since there is no internationally agreed definition. This might help the Parties come to an agreed definition that will help better define risk assessment and management actions.	See scope and methods for information on the scope of the document, which uses the operational definition.
Brazil	15	25	"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. **It is also recognized the conclusions of the AHTEG that the current synthetic biology organisms are LMOs and can be assessed using the case-by-case existing methodologies and in this case most of the examples described fall under the definition of LMO of Cartagena**".	Editorial suggestion noted.

Ecuador	15	07-09	The application of synthetic biotechnology does not necessarily yield GM products that meet this definition, for example, we could have products with gene deletion, gene overexpression, targeted mutagenesis, silencing; in this sense, the definition proposed in the Cartagena Protocol regarding "modern biotechnology" and "living modified organism" does not cover the range of possibilities of synthetic biology. It is suggested the elimination of the linkage of synthetic biology with the above mentioned definitions in the Cartagena Protocol.	See scope and methods for information on the scope of the document, which uses the operational definition.
South Africa	15	13 and 14	The lack of an international agreed-upon definition of ‘’Synthetic Biology’’ is a great concern. Without progress made on an agreed-upon definition, the content of the document is merely a suggestion according to the proposed definition suggested in lines 13 and 14 of page 15. It is suggested that the document be updated again after a clear definition is agreed upon internationally for Synthetic Biology.	Comment noted.
European Union	15	19-23	As mentioned above, we recommend to include this disclaimer also in Table 1.	Revision made.
Malaysia	15, 17	47, 11-25	A clear definition for Synthetic Biology and activities that comes under Synthetic Biology must be resolved to avoid duplication, misconception and understanding.	Revision made.
Brazil	17	24	“Similar to the divergent views on what is considered synthetic biology, there could also be different views on what could be considered a supporting technology or tool. This section provides information on some of the more widely used tools but is not meant to be an exhaustive list**, and is not meant that the use of those tolls will generate a synthetic biology organism**”.	Revision made.
Brazil	17	27	“Like the term “synthetic biology” under which it may fall, the term “gene drive” is most often used as if it were a single technology, but it is more accurate to consider each as a suite of approaches that can be tailored to the needs of specific applications.” It would be useful to have these different approaches that usually fall under the general scope of gene drive as a terminology described and defined.	Comment noted.

New Zealand	17	45	"synthetised" should be "synthesised"	Editorial suggestions noted and revisions made.
Malaysia	17	15,16,17	The phrase…"and the EU each one, is not very clear. Is it is meant to be one funder was identified from each of the EU member state? A rewording is suggested here. Suggestion would be….the UK, and one from South Korea and each of the EU Member state. Cross link with comment on pg 10 Lines 32/33/34	Revision made.
Malaysia	18	13	Remove parenthesis for Wang et al., 2009	Editorial suggestions noted and revisions made.
Malaysia	18	34	space between (ribonucleo)proteins	Editorial suggestions noted and revisions made.
Malaysia	18	37	Insert "are". changes and transgenic insertions are present	Editorial suggestions noted and revisions made.
Malaysia	18	01-03	The list of references must be updated regularly ie for eg examples: application lists. To get updated info which include reports from regulatory bodies as some of the related activities might still in the process of start off or mid-way and may not been published just yet.	General comment noted
Argentina	18	04-25	These two sections (point 1.2 and 1.3) should be revised, since it should include only those applications and outcomes relevant for synthetic biology.	General comment noted and revisions made
South Africa	18	28-29	No clarity if all synthetic biology product will be seen as GMO's or LMO's, the document refers to gene-editing technology that most countries have indicated, when used, will lead to products that will be a non-GMO product such as technologies mentioned in line 28-29 of page 18. If synthetic biology will be regarded as a GMO/LMO then the inclusion of these methods in the Technical Series should be reviewed.	General comment noted
Malaysia	19-24		To date, some of the technologies described here is still unavailable in Malaysia. However, with the advancement of this technology which is anticipated soon, our regulatory bodies must be ready with its regulation and governance and this includes updating and training of evaluators and decision makers.	General comment noted.
Malaysia	19	01	Why not name the 2 scientists who won the 2020 Nobel Prize in Chemistry? Emmanuelle Charpentier and Jennifer A. Doudna	Editorial suggestions noted and revisions made.

			https://www.nobelprize.org/prizes/chemistry/2020/press-release/ It is currently worded as "was awarded to developers of this tool". Compare with description of other Nobel Prize winners in Lines 11 & 12 of Page 20- it reads "of Andrew Fire and Craig Mello led to the 2006 Nobel Prize in Medicine (Nobel Media AB, 2021). Their names are mentioned. Compare also with another mention at Lines 24 and 25 of Page 23. Despite the ongoing patent dispute, it does not change the fact that the 2020 prize was awarded to them.	
Argentina	19	18	Targeted point mutations are not synthetic biology.	Comment noted. See scope and methods for clarity on the scope.
European Union	19	30	"… at the expense of their hosts". Is the spreading always at the cost of their hosts? This may be the case for population suppression strategies/systems but not necessarily for population modification strategies/systems	Editorial suggestions noted and revisions made.
Canada	19	31	It looks like the word "of" should be inserted between the words "populations" and "insects".	Editorial suggestions noted and revisions made.
Thailand	19	33	As the authors mentioned, "gene drive" is not a single technology but rather a suit of approaches, each of which has different levels of risk and capability. Thus, it is worth getting into a bit more detail on the range of existing approaches and ongoing discussion about how to utilize and regulate each of them.	General comment noted, no response required
European Union	19	27-28	Not sure that "circumvent" is the appropriate term to use. Given that gene drives occur naturally in a broad array of organisms, some authors (e.g. Hurst, 2019) have suggested that preferential inheritance may be the rule rather than the exception. Therefore, alternative wording may be helpful. Hurst LD, 2019. A century of bias in genetics and evolution. Heredity, 123, 33–43.	Revision made.
European Union	19	37-39	Perhaps the authors of the report may wish to cite relevant review papers here that provide an overview of the various engineered gene drives developed so far (instead of specific original research papers). Some relevant examples are given for convenience, below.	Revision made and references included.

			-Champer J, Buchman A and Akbari OS, 2016. Cheating evolution: engineering gene drives to manipulate the fate of wild populations. Nature Reviews Genetics, 17, 146–159. -Hay BA, Oberhofer G and Guo M, 2021. Engineering the composition and fate of wild populations with gene drive. Annual Review of Entomology, 66, 407–434. -Raban RR, Marshall JM and Akbari OS, 2020. Progress towards engineering gene drives for population control. Journal of Experimental Biology, 223, jeb208181.	
European Union	19	39-43	It would be helpful to consider the publication by Alphey et al. (2020) when addressing the definition and purpose of engineered gene drives. The reference to the publication is given below. Alphey LS, Crisanti A, Randazzo F, et al., 2020. Standardizing the definition of gene drive. PNAS, 117, 30864–30867	Revision made.
European Union	19	44-47	The list of currently proposed and/or developed engineered gene drives is incomplete. Additional designs with different or similar modes of action have been reported in the scientific literature (e.g. home and rescue gene drives, split rescue drive, underdominance gene drives). Perhaps the text could be updated accordingly, or could mention that the field is evolved rapidly and most likely yielding additional new designs and modes of action in the near future. Perhaps the authors of the report may also wish to consider Table 2 of EFSA (2020) for an overview/classification of current engineered gene drives in insects (see also WHO, 2021). -EFSA (European Food Safety Authority), 2020a. Scientific Opinion on the adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives. EFSA J. 18, 6297. -WHO (World Health Organization), 2021. Guidance framework for testing genetically modified mosquitoes, second edition. ISBN 978-92-4-002523-3. Available from: https://www.who.int/publications/i/item/9789240025233	Revision made.

European Union	19	44-47	"…, CRISPR-based homing gene drives are the most adaptable to new species and populations …". Can a rationale be provided to substantiate/clarify this statement?	Revision made.
Canada	20	10	It looks like the word "in" should be inserted between the words "present" and "almost".	Editorial suggestions noted and revisions made.
European Union	20	01-08	The concept of homing is not explained, though it is a key part of the message to convey. Perhaps a sentence could be added to explain homing	Editorial suggestions noted and revisions made.
New Zealand	21	07	"titter" should be "titre"	Editorial suggestions noted and revisions made.
Belgium	22	01	"DBTL" instead of "DBLT" in the title above the figure	Editorial suggestions noted and revisions made.
Argentina	23-29		The section "Areas of Synthetic Biology research" (whole point 2.) contains what authors consider as Synthetic Biology, but as we mentioned before there is no definition for synthetic biology. Besides, some of these areas mentioned are tools and others are applications.	Revision made
Malaysia	23	41	Remove "were". regulatory RNAs ~~were~~ have	Editorial suggestions noted and revisions made.
Ecuador	23	15-18	In this paragraph could be mentioned that directed evolution in the gene editing context, genetic engineering in silico, synthesis of molecules and metabolic engineering are also other areas of research in synthetic biology	Comment noted.
Argentina	25	14	"with classic genetic engineering techniques." – what is classic genetic engineering? As it is not clear, we recommend eliminating this term.	Revision made.
Canada	27	15	What does this first sentence mean? Vibrant but basic seems contradictory.	Editorial suggestions noted and revisions made.
Belgium	27	29	This work illustrates how *E.coli* can be engineered for the production of natural and non-natural flavonoid targets : Dunstan MS et al, (2020). Engineering Escherichia coli towards de novo production of gatekeeper (2S)-flavanones: naringenin, pinocembrin, eriodictyol and homoeriodictyol. Synthetic Biology, In Press, DOI: 10.1093/synbio/ysaa012	Comment noted
European Union	29	11	Would it help to describe the different potential applications first, irrespective of their development status, and then report on their	Comment noted.

			development status (including the Table)? This would enable to provide the full spectrum of potential applications currently proposed (even if hypothetical and only considered through population models), and avoid overlap in some of the subheadings presented (e.g. disease vector control applications: mosquitoes vs. ticks). Once all relevant potential applications have been presented, they could be ranked according to their development status and intended uses. Since the development status of the currently presented applications will evolve (rapidly), it may be more straightforward to describe the potential applications first, and subsequently rank them based on development status. The information provided in the report could easily be reshuffled accordingly. This approach may also ease regular updates of the report in the light of recent and new developments in the field	
European Union	29	35	For this category the word "commercially available" sounds strange as wild settings are usually managed by governments (as natural parks etc). Also we would expect for this category pro bono, sponsored or academic products.	Revision made.
Argentina	29	12-15	We consider that synthetic biology does not offer an "unprecedented toolbox" and several examples presented are not synthetic biology, as we mentioned before.	Comment noted
Belgium	29	01-28	The following reference could be added : https://www.nature.com/articles/s41589-020-00697-z	Comment noted.
European Union	29	31-33	The criteria used for the categorisation/ranking would benefit from being described in more detail, as this would add clarity and improve understanding. In this respect, there is a need to better to define what is meant with "confined field trials" and list concrete types of field trails that are considered "confined field trials". The terminology and classification used in the 2021 revised WHO framework for testing GM mosquitoes could be helpful to reproduce here and may ensure the use of standardised/harmonised terminology. WHO (World Health Organization), 2021. Guidance framework for testing	Comment noted

			genetically modified mosquitoes, second edition. ISBN 978-92-4-002523-3. Available from: https://www.who.int/publications/i/item/9789240025233	
European Union	30	27 + 41	There are different ways to contribute to conservation purposes. Therefore, could different categories of "conservation purposes" be given instead, under an overarching title "conservation purposes. Subheadings could be, for example, "applications for managing "unwanted/harmful/invasive" target species" and "improving the resilience of wild animal and plant populations"? Plus, could examples be given about possible engineered gene drives tailored towards (1) rescuing endangered species and (2) managing invasive species?	Revision made.
South Africa	31	13	There is also reference made to "Synthetic biology applications in semi-managed, managed, or urban settings" on page 31, line 13, which includes various examples of gene-edited crops without mentioning the method used to genome edit these crops, which lead to the conclusion that all genome-edited crops fall under the scope of Synthetic-Biology. Before a definition of synthetic biology is not agreed upon this cannot be concluded.	Please see scope and methods for clarification on the scope.
European Union	31	27	Are the examples given to be considered as deliberate releases into the environment for "commercial" or "experimental" purposes? Would some of the "self-limiting GM insect applications" listed here fall under "advanced development" category instead of "commercially available'? Note also that additional and more recent releases with self-limiting GM insects have been conducted; some of which may be relevant to mention for completeness. Plus, in the case of "self-limiting GM insects", no distinction is made between "disease vector" and "pest" control purposes, though such a separation is being introduced for engineered gene drive applications (some of which may also be considered as self-limiting GM insects). Note also that some GM insects with engineered gene drives are being designed to be self-limiting and localised. So by default, such systems could also be discussed under the "self-limiting GM insects" heading, so the headings used may benefit from further fune-tuning	Revision made.

Canada	31	05-10	Cloning is not typically considered "synthetic biology", so suggest re-considering the relevance of the example of the black-footed ferret presented here.	Revision made.
Argentina	31	14-32	We consider that none of the examples presented are synthetic biology applications (point 3.2.1)	Until consensus is achieved concerning which techniques, processes or products will fall under synthetic biology, there will always be a divergence of views and opinions on this amongst the readers (see Section B. Scope and Methods).
Canada	31	25-26	"Using Cibus' Rapid Trait Development SystemTM (ODM), Brassica napus acetohydroxyacid synthase 26 was mutated to confer tolerance to imidazolinone herbicides (Cibus, 2014; Schopke et al., 2008)." The description of a Cibus herbicide-tolerant canola product is inaccurate. Cibus' herbicide-tolerant canola Line 5715 contains a mutation that confers tolerance to a herbicide (sulfonylurea). While a gene editing technique known as oligonucleotide-directed mutagenesis (ODM) was used within the developer's Rapid Trait Development System™ (RTDS™), the mutation used in Event 5715 arose independently through spontaneous somaclonal variation. More information about the approved product can be found in this published CFIA Decision Document (2013-100), particularly under Section III. Description of the Novel Trait; 1. Development Method, and this published Health Canada document under 2. Development of the Modified Plant.	Revision made.
European Union	32	20	Why are these cases labelled differently than the "self-limiting insects" mentioned earlier in the report? In both cases, "self-limiting insects" are being addressed. Also note that the Oxitec cases mentioned above rely on the fsRIDL technique, so perhaps some alignment is needed to ensure consistency in wording used between both headings. The heading "Genetically engineered bio-containment systems in mosquitoes" is a bit confusing, as self-limiting/localised engineered gene drive systems are under development in insects, including mosquitoes,	Revision made.

			which would fit under this category too. CRISPR systems for genome engineering can also used to develop GM insect without engineered gene drive(s). Perhaps this point should be made more explicitly throughout the report	
European Union	32	6-8	Not sure why the term "organisms" is used in the introductory sentences. Perhaps the text could be made more specific by mentioning "disease-spreading mosquitoes" directly. Note also that more recent and relevant publications are available that could be cited here. Connolly JB, Mumford JD, Fuchs S et al (2021) Systematic identification of plausible pathways to harm via problem formulation for investigational releases of a population suppression gene drive to control the human malaria vector Anopheles gambiae in West Africa. Malar Journal, doi:10.1186/s12936-021-03674-6	Revision made.
European Union	32	16-19	Is this work to be considered as "research" or "advanced development"? The criteria used for the categorisation could be better clarified to add clarity. Have "confined field trials" been conducted for the application list here?	Revisions made.
Republic of Korea	33	10	Geddes et al. (2019)recently → Geddes et al. (2019) recently	Editorial suggestions noted and revisions made.
New Zealand	33	31	"*Arabisopsis"* should be "*Arabidopsis"*	Editorial suggestions noted and revisions made.
Argentina	34	08	(d) "Transient modification of agricultural plants through RNAi spray or nanomaterials" – this is not synthetic biology.	Comment noted. See scope and methods for clarification on scope.
Malaysia	34	29	Replace "an" with "a". Julve Parreño et al (2018) described a synthetic biology approach	Editorial suggestions noted and revisions made.
Belgium	34	39	In the area of CAR T-cells therapy, allogeneic CAR- T cell therapy has the potential to pave the way for further breakthrough in the treatment of cancer. See Depil et al., 2020, Nature reviews Drug Discovery 19, 185-199 (2020). Research in this area could be mentioned when addressing advances in clinical therapeutics.	Comment noted.

Republic of Korea	35	27	Greenhouse and waste gas (CO_2, CO, CH_3) → Greenhouse and waste gas (CO_2, CO, CH_4)	Editorial suggestions noted and revisions made.
Malaysia	35	30	Replace the word "excepted" to "expected". The products are expected to increase	Editorial suggestions noted and revisions made.
Malaysia	35	9, 10	Grammar edit, ...the protein was engineered to become active upon binding to a bacterial endotoxin.	Editorial suggestions noted and revisions made.
New Zealand	36	05	"tomelting" should be "to melting"	Editorial suggestions noted and revisions made.
Malaysia	37	07	Typo. Novel CRISPR proteins	Revision made
European Union	38	21	For engineered gene drive applications in insects, perhaps more emphasis should be put on the new modes of action and underlying strategies that are currently proposed and reported in the scientific literature. In this respect, it would be important to mention that recent research efforts aim to develop engineered gene drives that are confinable (i.e. limited in their spread and persistence) and reversible (i.e. recallable from the environment in the event of unwanted consequences). Several approaches have been proposed to restrict the spread of engineered gene drives within a specified target population or geographic region, or to reduce their persistence in target populations over the course of several generation. Likewise, reversal gene drive have been proposed as genetic remediation or neutralising systems that could disable or reverse the effects of a previously released gene drive modified organisms in the event of unintended consequences. Perhaps these developments could be mentioned in the report. Moreover, it may be helpful to indicate that current research efforts also focus on the development of engineered gene drives that are specific, stable and avoid or delay the evolution of resistance against them	Risk mitigation approach are developed in section 4.1
Malaysia	39	12	Add the word "of" prevent transfer of transgenic information	Editorial suggestions noted and revisions made.

Canada	40	01	Formatting, “Lin et al. (2020)reviewed” has 2 instances of incorrect spacing.	Editorial suggestions noted and revisions made.
Republic of Korea	40	01	and Lin et al. (2020)reviewed → and Lin et al. (2020) reviewed	Editorial suggestions noted and revisions made.
Canada	40	03	Formatting, incorrect spacing “levels(Wan…”	Editorial suggestions noted and revisions made.
Republic of Korea	40	03	levels(Wan et al., 2019). → levels (Wan et al., 2019).	Editorial suggestions noted and revisions made.
Republic of Korea	40	05-	Would it be possible to provide reasons why certain applications of synthetic biology have remained in early stages of R&D? Because of technical difficulties? Lack of funding? Too much regulation?	Comment noted.
Argentina	40	25-29	In everything mentioned in the paragraph there are no examples of synthetic biology.	Until consensus is achieved concerning which techniques, processes or products will fall under synthetic biology, there will always be a divergence of views and opinions on this amongst the readers (see Section B. Scope and Methods).
Brazil	41	04-05	“Sustainable use **can** encompass~~es~~ ecological, economic, social, cultural, and political factors (Glowka et al., 1994)”.	Editorial suggestion noted.
Brazil	41	09	“Likewise, synthetic biology applications can raise social, economic, and cultural considerations which are equally important for decision-making and governance of the issue **if applicable, in a case-by-case basis**”.	Editorial suggestions noted and revisions made.
European Union	41	11-12	There is substantial overlap of information reported in section 4 “Applications of Synthetic Biology and Their Potential Impacts on the Conservation and Sustainable 11 Use of Biological Diversity” and the previous section of the report. To avoid unnecessary duplications, perhaps the intended impacts on ‘wild’ target populations of potential SynBio applications (and thus their intended outcomes) could be merged and addressed in the section C instead of section D. For example, the types of engineered gene drives should be described in section C instead of section D. The potential impacts/risk concerns are addressed in a narrative and non-systematic manner, and tend to be generalisations. Moreover, risk concerns are addressed as plain text without subheadings. For clarity and readability	Comment noted. Revisions made.

			purposes, perhaps it may be helpful to introduce subheadings for relevant groups of risk concerns. For each of these risk concerns perhaps it could be specified whether the risk concerns identified are plausible or not, consequential in terms of harm to human and animal health and the environment, and specific to the case under assessment or not. The lack of efficacy of an engineered gene drive could lead to harm, and thus should be addressed explicitly in the report. Perhaps the authors of the report may wish to follow a more systematic approach for the identification of risk concerns and assess whether they are plausible and consequential. The pathway to potential harm approach could be followed for this purpose. See for example Connolly et al. (2021). Connolly JB, Mumford JD, Fuchs S et al (2021) Systematic identification of plausible pathways to harm via problem formulation for investigational releases of a population suppression gene drive to control the human malaria vector Anopheles gambiae in West Africa. Malar Journal, doi:10.1186/s12936-021-03674-6	
European Union	41	31-32	The scope of "conservation purposes" should be better defined in the report	Revision made.
European Union	41	35	The rationale for focusing on engineered gene drives in this section is not entirely clear, especially in the light of other genetic control approaches that may involve elements of the SynBio toolkit for their engineering/development. Moreover, it seems that the examples given are not all up to date, and that relevant scientific publications, including more recent ones, are not cited. Hence, it would be helpful to cite additional relevant scientific publications, including more recent ones, throughout this section. In this respect, specific emphasis could be given to the revised WHO guidance framework for testing GM mosquitoes. Some of the points raised are not specific to engineered gene drives, and apply to other biological, genetic and chemical disease vector/pest control approaches. Perhaps it would be helpful to focus the text on new or different harms associated with the potential use of engineered gene drives, and distinguish them from similar harms caused by current disease vector/pest control approaches. A way to achieve this is to describe the "novel features" of engineered gene drives as compared with other (current	Comment noted. Revisions made. The WHO guidance framework is described in other parts of the document.

			and emerging) disease vector/pest control systems at the beginning of the section to frame the rest of the text better, and enable focusing the text on key differences between engineered gene drive-based systems and other disease vector/pest control ones (see also EFSA GMO Panel, 2020). -EFSA (European Food Safety Authority), 2020a. Scientific Opinion on the adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives. EFSA J. 18, 6297. -WHO (World Health Organization), 2021. Guidance framework for testing genetically modified mosquitoes, second edition. ISBN 978-92-4-002523-3. Available from: https://www.who.int/publications/i/item/9789240025233	
European Union	41	36-37	Not all the intended uses listed here are specific to GM insects with engineered gene drives. Other (novel) genetic control approaches have more or less similar goals. Perhaps this point could be acknowledged more explicitly?	Comment noted. Revisions made.
Thailand	41	38	Risk & benefit assessment of using gene drives to target invasive alien species (IAS) should be done in the context of other countermeasure approaches (such as the use of chemicals or ecological manipulation approaches) as well as comparing to the risk of benefit of taking no action. There should be more discussion these topics.	Comment noted. Revisions made.
European Union	41	38-39	What about the potential to help rescue endangered species?	Comment noted.
South Africa	42	08, 28	The reference list need to be checked. It was noted that the reference for Reynolds (2020) was incorrectly cited and referenced as Reynolds 2021 when it should be Reynolds (2020). This same reference was also cited as Reynolds 2021b which does not appear in the reference list. This error was found by co-incidence, therefore, it is recommended that the entire reference list be checked for errors.	Revisions made.
United States of America	42	17-24	We recommend deletion or clarification for the statements below. In the context of the section, the release of genome-edited or gene-drive modified organisms is meant to control or suppress a species population within a	Editorial suggestion noted and revision made.

			region, which nullifies the concerns of the statements below. IAS management applications are not applicable to native species populations. If the text is retained, suggested edits are shown in red below. "It is therefore possible that under certain circumstances, conservation gains from these uses could be offset or even outweighed by associated conservation losses elsewhere, for example if the target species is native or performs an essential role in community structure and/or ecosystem dynamics (Redford et al., 2019)). Further, depending on the type and scale of the modification, IAS management synthetic biology applications ~~gene-edited organisms~~ released into the environment for instance, could also result in unwanted impacts on biodiversity, including off-target mutations, evolutionary resistance, ecological disturbance and extinctions; each of which have triggered a heated discussion regarding their environmental impacts and regulatory oversight (Esvelt et al., 2014; Kofler et al., 2018; Romeis et al., 2020)."	
European Union	42	20-24	Off-target mutations do not constitute per se an unwanted impact on biodiversity. We suggest to delete "off-target mutations". To consider possible impacts of off-target mutations, we suggest to amend the beginning of the sentence as follows: "Further, depending on the type and scale of the intended and unintended modifications,…"	Editorial suggestion noted and revision made.
United States of America	42	25-26	We suggested the text edits in red below to reflect that the technology used to develop gene drive-modified organisms is not relevant. We recommend that this be reflected throughout the document. If the authors believe that there is an appreciable difference between CRIPSR and non-CRISPR gene drive-modified organisms, we recommend that this be explicitly discussed. "Engineered gene drive systems~~, notably CRISPR–Cas9 gene drives,~~ have recently emerged with potential applications not only in conservation but also in public health and agriculture (López Del Amo et al., 2020)."	Editorial suggestion noted and revision made.
United States of America	43	04-08	We recommend deletion of this statement. Applications of many technologies may have ancillary, downstream effects on biodiversity that are completely unrelated to the original application and sets an unwarranted precedent that evaluates decreased public health risks with increase	Revision made.

			biodiversity conservation risks. ~~"Further, although not specific to synthetic biology approaches, the reduction or elimination of human malaria from 6 geographical areas may lead to demographic and land-use changes, potentially impacting biodiversity conservation (Redford et al. 2019)."~~	
Brazil	43	32-33	There is not enough scientific evidence for this statement. "~~However, recent research indicates that engineered gene drives may face resistance and limited efficacy in wild mosquito populations~~".	Comment noted.
European Union	43	32-45	The text does not explore how loss of engineered gene drive efficacy could result in harm. Perhaps this requires further consideration. Moreover, it would be helpful to mention to which extent the potential for resistance to evolve is higher, similar or lower for engineered gene drive systems compared to other disease vector/pest control systems	Comment noted.
European Union	44	01-10	The points raised are not specific to engineered gene drives, but also apply to other disease vector/pest control strategies. It would therefore be important to underline more explicitly what novel features of engineered gene drives may cause more or different harms compared to currently used control systems	Comment noted.
European Union	44	11-24	It may be helpful to address the potential spread and persistence characteristics of engineered gene drives at the beginning of the section instead of at the end	Revision made.
Brazil	44	22-23	Delete the end of line 23, that presents an incorrect generalisation. The risk assessment is carried out on a case-by-case basis, "Given that organisms containing engineered gene drives can potentially impact biodiversity, national sovereignty and food security, there is a crucial need to develop strategies to minimise to evaluate any potential risk, including those of intentional and unintentional spread and to mitigate harm to humans or the environment (de Wit, 2019; DiCarlo et al., 2015; National Academies of Sciences Engineering and Medicine, 2016).	Comment noted and text revised.

Argentina	44	30-31	"and that provide alternative weed control (e.g. Cibus' oilseed rape resistant to CLEARFIELD® herbicides" – these examples are not synthetic biology.	Comment noted and text revised.
European Union	44	35-40	Several impacts mentioned in this paragraph have been considered, but not really observed from analogous applications exploiting genetic modification technology in agriculture. We suggest to replace "observed" with "considered".	Comment noted and text revised.
European Union	44	41-46	As reported later in the text, "mutagenesis techniques used in conventional breeding are rife with off-target effects…" (page 45, lines 6-7). Therefore, we suggest to amend the text here as follows: "again, phenomena that have been reported with classical genetic engineering as well as conventional breeding".	Editorial suggestion noted and revision made.
Argentina	44, 45	41-48, 1-19	Genome edited plants are not examples of synthetic biology, they should be deleted (p. 44, lines 47- 48; p. 45, lines 1-4). See comment above on off targets Delete the paragraph on p. 45, 5-19, since it is not relevant to synthetic biology.	See scope and methods for clarity on the scope of the document.
Brazil	44	44	"Some of the techniques of genome editing (that for some may not fall under synthetic biology; see Scope & Methods) are less precise than others such that additional molecular changes to the intended (i.e. off-target modifications) can also be introduced into the host organism; again, phenomena that have been reported with ~~classical genetic engineering~~ **modern biotechnology** (Eckerstorfer, Heissenberger, et al., 2019)".	Comment noted and revision made.
European Union	45	09	We believe that an important consideration has not been reported in the document and we suggest to include the following: "Experimental evidence indicates that off-target mutations potentially induced by genome editing techniques are of the same type as those mutations obtained through conventional breeding (EFSA Panel on Genetically Modified Organisms (GMO), 'Applicability of the EFSA Opinion on SDNs type 3 for the safety assessment of plants developed using SDNs type 1 and 2 and	Comment noted and revision mad.

			oligonucleotide-directed mutagenesis', EFSA Journal 2020;18(11):6299. doi:10.2903/j.efsa.2020.6299).	
European Union	45	11-13	We believe that the sentence, as it is formulated, does not reflect fully the statement of the European Commission High Level Group of Scientific Advisors 2017.We suggest to amend the sentence as follows: " Those off-target changes that remain may or may not lead to phenotypic effects…"	Comment noted and revision made.
United States of America	45	11-16	We recommend that these statements be deleted. As described in lines 5-11, off- target changes to the genome are noted to occur during conventional breeding processes at rates similar to or below that of genome-editing techniques and that these changes can be effectively removed through back-crossing and that genome- editing does not lead to enhanced risk in comparison to conventional methods. ~~"Those off-target changes that remain may lead to phenotypic effects affecting the properties of the modified organism (European Commission High Level Group of Scientific Advisors, 2017), and have the potential to ultimately lead to alterations of population characteristics, especially when spread amongst individuals via gene transfer. This may ultimately lead to unintended or unexpected consequences during interactions with associated species or populations in the surrounding environment."~~	Comment noted and revision made.
Canada	45	16-19	"Conversely, the cause of some of this imprecision is also being exploited by developers to intentionally modify more than one related sequence (with less than 100 percent sequence identity) in attempts to modify different alleles or homologous genes in the host organism at the same time (Lema, 2021)" The Lema 2021 paper is cited in the report, but there is no discussion on the methods proposed within to detect and regulate off-target DNA changes following genome editing: Bioinformatics identification of potential off target sites can be combined with whole genome sequencing (or directed sequencing) to confidently identify both small genetic changes and larger insertions or rearrangements.	Revision made.

Malaysia	46	16	Remove one full stop. 2020; Spalding & Brown, 2015)..	Editorial suggestion noted and revision made.
Brazil	46	29-37	Delete all the paragraph. Only peer reviewed literature should be used as a reference. ~~"Potential negative impacts could result from the increased utilisation of biomass for synthetic biology applications. "Biomass" is generally used to refer to the use of "non-fossilised biological and waste materials as a feedstock" (ETC Group, 2011; Jeswani et al., 2020). Additionally, potential negative impacts include the displacement of sustainable uses of biomass, the destruction of native forests and marginal" lands such as deserts and wetlands to provide land to establish plantations for biomass production, and harvesting of biomass from natural grasslands (ETC Group, 2010; Royal Academy of Engineering, 2017). On balance, many anticipate that the potential efficiencies and attendant reduction in reliance on fossil fuels offered by energy production using synthetic biology would offset anticipated risks to the environmental ecosystem as it exists today. But considerable uncertainty remains (ETC Group, 2015)".~~	See scope and methods section for clarity.
United States of America	46	29-30	We suggest the text edits in red below to reflect that these concerns are linked to arable land usage derived from first-generation biomass applications. We note that biomass applications not associated with arable land use do not have the same implications. "Potential negative impacts could result from the increased utilisation of biomass derived from first generation synthetic biology applications that require arable land."	Comment noted.
Republic of Korea	46	41	Should consider biocontainment methods developed by synthetic biology	Comment noted.
Argentina	46	41-46	Consider delete "off target modifications", since scientific publications consider that off target mutations are fewer in edited organisms that in conventionally bred organisms.	Comment noted.
Brazil	47	17-20	Delete from line 17 to line 20. Only peer reviewed literature should be used as a reference. ~~"Additional examples from Section 3 include the production of~~	See scope and methods section for clarity.

			~~recombinant Factor C (rFC) from synthetic horseshoe crab blood, synthetic rhinoceros horns and squalene, each of which could reduce or remove the need to exploit wild species (ETC Group, 2013; Woodrow Wilson International Center for Scholars, 2012)".~~	
United States of America	47	23-25	We recommend that further information be provided to clarify how replacement of natural products with synbio products would disrupt in situ conservation projects. "However, the situation is a little more nuanced than originally expected. For example, the replacement of 23 natural products with products resulting from synthetic biology could lessen the pressure on natural habitats 24 but could also disrupt in situ conservation projects."	Revision made.
Brazil	47	31-36	Delete from line 31 to line 36. Only peer reviewed literature should be used as a reference. ~~"One case where real-life experience has been gained concerns vanillin. Initially, the production of vanillin by synthetic biology (Section 3.3.1(d)) arose concerns that its large-scale production could negatively impact the many smallholder farmers involved in the production of cured vanilla beans (ETC Group, 2013). Vanilla orchids are commonly produced by inter-cropping with rainforest trees as 'tutors' for vanilla vines to grow on, and so it was thought that reduced demand for the natural product could disrupt this agro- ecological method of cultivation (ETC Group, 2013)".~~	See scope and methods for clarity.
Thailand	47	40-41	It would be nice to elaborate on public opinion / consumer perceptions regarding bio-compounds derived from nature vs synthetic chemistry vs synthetic biology approaches.	Comment noted.
Brazil	47	46-47	"The use of synthetic biology triggers a wide variety of views related to perceptions of risks and benefits, moral and ethical values, along with broader issues such as socio-economic aspects. **Risk assessment is a science-based procedure to estimate the risks and to define risk management strategies while the decision-making can consider other factors, according with national legislations and circumstances.** ~~A science-based assessment of impacts is therefore seen as part of a wider~~	Editorial suggestion noted and revision made.

			~~decision-making activity; one that evaluates such economic, political, moral and ethical concerns alongside scientific predictions of changes that would result from using technology~~".	
Brazil	48	01	"**Voluntary ~~G~~g**uidance ~~on the process for assessing such concerns has recently emerged~~ **about socio economic considerations is available** (Secretariat of the Convention on Biological Diversity, 2018), especially with regard to the value of biological diversity to indigenous peoples and local communities".	Editorial suggestion noted and revision made.
United States of America	48	15-18	As currently written, this statement implies that existing risk assessment and management strategies across the board are not fit for use and need to be revised and we recommend amending the sentence so it is focuses on facts and science. "However, the degree to which a risk is acceptable cannot be determined purely scientifically; science can predict the likelihood of certain effects, but non- scientific criteria must be included in the process of judging their acceptability (Johnson et 17 al., 2007)."	Comment noted.
United States of America	48	28-29	We recommend the addition of further information. The text does not make clear whether these emerging technologies and their applications are actively discussed by the research community, industry, and conservation societies. We recommend including more detail on the current gaps. Suggested text edits in red below. "As suggested by Oye et al. (2014), for applications of emerging technologies that affect the global commons, concepts and applications should be published in advance of construction, testing, and release."	Editorial suggestion noted and revision made.
United States of America	48	35-39	Suggested text edits in red below. We note that "NBT" is not a well-defined term and is not used consistently throughout the document. "This same approach continues to be echoed, for example in a recent survey of experts (Lassoued et al., 2019) in which the majority indicated that the regulations for health and safety, followed by export markets, consumers, and the media play a major role in determining where and how newer genetic engineering technologies~~New Breeding Techniques~~ (Obukosia et	Editorial suggestion noted.

			al., 2020; Seyran & Craig, 2018), including genome editing, will be developed and used in agriculture."	
Thailand	48	37-39	We would love to see more statistics and trends regarding public acceptance of different kinds of synthetic biology technologies and products.	Comment noted and text added.
Canada	48	39-43	"Society as a whole therefore has a key role to play in helping decision-makers and regulators better define specific protection goals (or "assessment endpoints") i.e. the things that society doesn't want harmed (Section 6.), that then dictates the characteristics of new products or technologies from synthetic biology to be assessed both scientifically (Craig et al., 2017) and socio-economically (Secretariat of the Convention on Biological Diversity, 2018)." Although society as a whole can help decision makers and regulators better define protection goals, please note the scope of Article 26* of the Cartagena Protocol, where Parties may take into account Socio-economic considerations (SECs): • arising from the impact of LMOs, • limited to the conservation and sustainable use of biological diversity • consistent with international obligations SECs could influence risk management, but the assessment of SECs should not be part of the risk assessment process, which should be based in science. The use of non-science based approaches to evaluating SEC of LMOs, if applied exclusively in risk assessments, could lead to an inconsistency with WTO obligations. *Article 26 The parties, in reaching a decision on import under this Protocol or under its domestic measures implementing the Protocol, may take into account, consistent with their international obligations, socio-economic considerations arising from the impact of LMOs on the conservation and sustainable use of biological diversity, especially with regard to the value of biological diversity to indigenous and local communities.	Revision made.
Brazil	48	41	Delete from line 36 to line 40. Only peer reviewed literature should be used as a reference. ~~"The displacement of some of the natural products (i.e. naturally occurring molecules obtained from plants) can potentially ease negative pressures on~~	See scope and methods for clarity.

			~~wild or cultivated species, but it can also displace cultivation practices, often in topical and sub-tropical regions. If not handled sensitively, this therefore may bring them into conflict with, or displace, those naturally sourced products which underpin the livelihoods and fragile economies of smallholder producers (ETC Group, 2016; ETC Group & Fibershed, 2018; UNCTAD, 2019)".~~	
United States of America	50	12-15	Suggested text edits in red below to reflect that socioeconomic factors are not a component of a risk assessment. "Additionally, how IPLCs perceive nature, the unique way that they interact with it, and how this can be captured by the global regulatory governance and regulatory scheme, as well as in the risk analysis and management~~assessment~~ of impacts associated with synthetic biology, each present unique challenges that must be considered and overcome in relation to FPIC."	Editorial suggestion noted and revision made.
European Union	50	29-32	The statement is not applicable to all engineered gene drive approaches (e.g. self-limiting/localised systems) and should be revised	Comment noted.
United States of America	51	11-12	We recommend inclusion of a citation for this statement. "The different fundamental objectives of the international trade and 11 environmental regimes have led to conflicts in the regulatory measures taken to achieve these objectives."	Comment noted and revision made.
United States of America	51	15-19	We recommend increasing the clarity of these statements. "...impacts of handling" needs to be expanded to describe what is being handled – applications of synthetic biology? The text does not make clear how many studies are required and this could usefully be clarified, e.g., do we mean one study for each potential product? "Further, it has been recently suggested that decision-makers may need formal and quantitative studies on potential economic impacts of handling, for example genome-edited products, under different regulatory scenarios. Such studies would allow them to weigh the impact of different regulatory/policy-making options on the economy (considering trade, agro-industrial innovation 18 and productivity) (Whelan & Lema, 2017)."	Comment noted.

United States of America	51	19-21	The meaning of this statement, especially in relation to what is being indicated by "interpretative flexibility" is unclear and we suggest enhancing the clarity by revising the sentence. "A formal analysis of the trajectory or dynamics that the interpretative flexibility is taking may be useful to anticipate the social perception of these decisions (Duensing et al., 2018)."	Comment noted and text revised.
Malaysia	51	30	Remove parenthesis ...this appear to be United Nations Conference on Trade and Development, 2019:	Editorial suggestion noted.
Brazil	51	36-40	Delete from line 36 to line 40. Only peer reviewed literature should be used as a reference. ~~"The displacement of some of the natural products (i.e. naturally occurring molecules obtained from plants) can potentially ease negative pressures on wild or cultivated species, but it can also displace cultivation practices, often in topical and sub-tropical regions. If not handled sensitively, this therefore may bring them into conflict with, or displace, those naturally sourced products which underpin the livelihoods and fragile economies of smallholder producers (ETC Group, 2016; ETC Group & Fibershed, 2018; UNCTAD, 2019)".~~	See scope and methods for clarity.
Canada	51	40	Double closed parentheses at the end of the line.	Editorial suggestions noted and revisions made.
Ecuador	52	10	It is suggested that "real thing" be replaced by "non-synthetic product".	Editorial suggestion noted and revision made.
Canada	52	16-17	How did they come to the conclusion? Brief reasoning would help clarify, as previous lines indicate that the effect of synthetic alternatives are not clear with regards to the impacts on poaching.	Comment noted and text revised.
United States of America	52-53	44-49, 1-7	We consider that this paragraph is largely speculative and we did not see evidence to support the stated concerns. Most associated references are 8+ years old – with the continued use of synbio applications, is there more recent evidence to support that the speculated effects have been realized? "Questions of synthetic biology's impact on attitudes to biodiversity and	Comment noted.

			conservation continue to be asked, especially around how synthetic biology will change public perceptions of what is natural, and if it will "challenge the ethical basis for conservation action" (Redford et al., 2013). It has been speculated that synthetic biology could "encourage an inaccurate model of biodiversity protection as maintaining an inventory of biological units" (Norton, 2010). Building on this, Redford et al. (2013) noted the increasing importance of ecosystem services in valuing biodiversity, and asked what will happen if ecosystems with synthesised elements are able to out-compete natural ecosystems, "delivering more services with less biodiversity". More recently, the debate about the potential use of synthetic biology with engineered gene drives have raised concerns not only about the potential impacts on biodiversity, but also ethical concerns about who will/should decide on the use of an application that could potentially spread across national borders. The scenario of a country approving the application and neighbouring country restricting its use is feasible and raises questions about governance and ethical issues that could be also related with the FPIC (see Section 7.1.2)."	
United States of America	53	11-13	We consider that this paragraph is largely speculative and we did not see evidence to support the stated concerns. Associated references are 10+ years old – with the continued use of synbio applications, is there more recent evidence to support that the speculated effects have been realized? "The application of intellectual property rights to synthetic biology, such as patents on DNA sequences or organisms resulting from synthetic biology, could restrict the global distribution of products and knowledge (ENCH, 2010; ICSWGSB, 2011; Schmidt, 2009)."	Comment noted.
Brazil	53	14-16	"~~Civil society groups strongly critique the way that IP regimes have been used in agricultural biotechnology to concentrate power with a few corporations, and they see similar patterns of use occurring in synthetic biology (ICSWGSB, 2011; ETC Group, 2010; Friends of the Earth, 2010)~~".	See Scope & Methods section.
United States of America	53	35-50	The implications of this paragraph are unclear and in our view it lacks a clear rationale that supports an outcome to the provided information. We recommend either greater clarification be provided regarding the point of the paragraph or its deletion from the document.	Comment noted.

			"Common considerations have for instance included the ethical debate on whether to ban publications of dual use science discoveries and whether synthetic biologists are "playing God" (Boldt & Müller, 2008; Douglas & Savulescu, 2010; Kaebnick, 2009; The Royal Academy of Engineering, 2009). However, for some, "playing God" may not be regarded as problematical. One could argue that humans are the God species and should take control over natural processes in order to achieve human flourishing on this planet (Bovenkerk & Nijland, 2017). Thus, the role of human intervention in nature and natural processes, including this idea of naturalness have been raised as there could be a greater need to understand our values of nature, goals for conservation and the promise of biotechnology (Graeff et al., 2019). With the advent of new technologies, the biophysical influence of humans on nature could be more profound, having implications on biological evolution by controlling whole ecosystems and species (Graeff et al., 2019; Kaebnick, 2009). For example, editing a gene which has evolved over thousands of years could be viewed as a disruption to natural homeostasis (Šutković et al., 2020). Further, in the case of modifying genomes, the idea of integrity could be challenged with our understanding of how a genome constitutes an organism (Bovenkerk & Nijland, 2017). Another common consideration around the possibilities to either using this technology irresponsibly and cause harm, or not using it at all, which could also prove damaging to humans, our welfare, and our planet (Kofler et al., 2018)."	
United States of America	54	02-04	We have made suggested text edits in red below to reflect that there is broad support for this view, as well as specifically pinpointing the exact techniques. SynBio techniques are inconsistently associated with only genome editing techniques in the document and we recommend that this be reviewed and corrected within the text. "A number of researchers, policymakers, and regulators~~Some could~~ view the application of some genome-editing~~synthetic biology~~ techniques as analogous to selective breeding, especially in cases where species-specific function is not hampered (Bovenkerk & Nijland, 2017)."	Editorial suggestion noted.

United States of America	54	17-20	We recommend inclusion of a reference for this statement. "The optimism expressed by some is not shared by all members of the conservation community, with some expressing deep concern that applications of synthetic biology may serve as "Trojan horses" for other "more questionable" applications."	Comment noted and revision made.
United States of America	54	23-25	We recommend that the statement below be reframed, supported with further evidence, or be deleted from the document, as it directly contradicts the previous sentence, which states that "policy debate to be grounded... impartial standards that are free from ideology or political bias..." "There therefore remains a large scope for society to be further involved in formative discussions concerning the acceptability or otherwise, and thus consequently the regulation of synthetic biology applications and products."	Comment noted.
South Africa	54	27-28	The potential use of synthetic biology for bioterrorism, biological warfare and the construction of novel organisms designed to be hostile to human highlights the need to bring on board ministries responsible for this in the regulatory system	Comment noted.
United States of America	54	27-47	We consider that this paragraph could usefully be put into context with the relevant international instruments and standards that relate to hostile use of biological materials, such as the Bioweapons Convention. Without this appropriate context, in our view this section may imply that new approaches are necessary to address the listed concerns. "Bioterrorism, biological warfare and the construction of novel organisms designed to be hostile to human interests can all potentially be achieved through the malicious (or dual-) use of synthetic biology. Bioterrorists might, for example, create new pathogenic strains or organisms resistant to existing defences. Currently, it is possible to enhance the virulence of known pathogens with new traits that can contribute to their competence and resistance to existing treatments. For example, a novel type of avian flu virus with enhanced infectivity in mammalian animals may be created, and the H5N1 virus can be modified to evolve into a dangerous human virus (Herfst et al., 2012). It has even been suggested that pathogens might be engineered to attack only a particular genetic subset of a population (Garfinkel et al., 2007). Likewise, Mukunda et al. (2009) predicted that	Discussions at the international level are explored more fully in Section 9.

			biological weapons customised to attack specific groups were highly likely to be developed in the long term (10 or more years), i.e. the period between the previous technical series document and this update. Although microbes are usually the main platform for the development of applications with malicious intent, plants are not immune to such approaches. It has been recently suggested 38 that criminals may exploit modern gene editing technologies to subject market GMOs to clandestine manipulation (or the malicious insertion of genetic modifications into ostensibly unmodified plants), raising the prospect not only of direct harm, but of the more likely effects in generating public concern, reputational harm of agricultural biotechnology companies, lawsuits, and increased import bans of certain plants or their derived products (Mueller, 2019). It has been further suggested that when (mis-)used, especially in combination with newer technologies such as engineered gene drives, virus-mediated methods, or in vitro evolution techniques, the effectiveness of current authentication and surveillance protocols may be overridden. Unfortunately, it is by no means clear that such abuses could be entirely eliminated, any more than they can be for other 'dual-use' technologies."	
United States of America	54	34-37	We consider that this paragraph is largely speculative and we did not see evidence to support the stated concerns. Associated references are 10+ years old – with the continued use of synbio applications, is there more recent evidence to support that the speculated effects have been realized? "Likewise, Mukunda et al. (2009) predicted that biological weapons customised to attack specific groups were highly likely to be developed in the long term (10 or more years), i.e. the period between the previous technical series document and this update."	Comment noted and revision made.
Thailand	55	20-21	The real harms inflicted by biohackers might be small (given their limited proficiency/experience/resources). However, these activities could do serious damages on the public perception on the scientific community and the field in general. How have the policymaker, academia and industry planned to prevent/mitigate that?	Comment noted and revision made.
Saint Lucia	55	25	More options need to be given on the ways to prevent 'bio-hacking'	Comment noted and revision made.

European Union	56	01-08	The flow of arguments given is challenging to follow/grasp. Plus, some of the statements made a rather vague/cryptic "different methods and techniques of synthetic biology may need different forms and levels of oversight" and thus not helpful	Comment noted and text added to sentence following statement.
European Union	56	45	General comment on 6.1:This section should be improved and become more factual. The section focuses only on gene drives, genome editing and RNA-based technologies and lacks any consideration on other Synbio applications that are relevant within this context. Please note that the two recent EFSA opinions on synthetic biology plants (https://www.efsa.europa.eu/en/efsajournal/pub/6301) and microorganisms (https://www.efsa.europa.eu/en/efsajournal/pub/6263) cover a wider range of synbio products. The ones of microorganisms also include metabolic engineering and xenobionts. The practical examples there demonstrate more systematically and in detail the adequacy of risk assessment methodologies. We therefore recommend to expand the scope of section 6.1 to cover other relevant Synbio areas (e.g. xenobiology).	Revision made.
Malaysia	56	46	Remove full stop (Section 3.)	Editorial suggestion noted.
United States of America	56-57	47-48, 1	We are not clear what is meant by "completely new organism"? We recommend including more detail, as well as references to clarify the intent of this text. "While some might present less complexity and novelty compared to those produced by other methods or those coming for example from genetic engineering (i.e. LMOs), some might represent a completely new organism."	Comment noted and revision made.
United States of America	57	02-03	We suggest the text edits in red below to reflect that socioeconomic factors are not a component of a risk assessment. "Therefore, the adequacy of current methodologies for the environmental risk management and analysis ~~assessment~~ of synthetic biology products might depend on how their novelty and complexity is perceived (Wikmark et al., 2016)."	Editorial suggestion noted and revision made.

Brazil	57	03-06	"~~Different methods and techniques of synthetic biology may need different forms and levels of oversight. Thus, any new risk assessments, cost-benefit analyses and regulations must flexibly encompass different applications, uses and products (ETC Group, 2012)~~".	See Scope & Methods section.
United States of America	57	03-07	We suggest text edits in red below to reflect that the focus is on applications and not techniques. We recommend the inclusion of more information on the need for different forms and levels of oversight for different synbio applications. It would be useful to clarify which applications fall outside of current regulatory scopes. "Applications developed using d~~D~~ifferent methods and techniques of synthetic biology may need different forms and levels of oversight. Thus, any new risk assessments, cost-benefit analyses and regulations must flexibly encompass different applications~~, uses and products~~ (ETC Group, 2012)."	Editorial suggestion noted.
European Union	57	04-06	We propose to replace 'new risk assessment' by 'new risk assessment framework	Editorial suggestion noted and revision made.
European Union	57	12-13	'The process should include mechanisms that facilitate the effective engagement of stakeholders and help integrate these considerations within the overall decision-making process' This would benefit from concrete examples where it has been successfully accomplished.	Comment noted.
European Union	57	14-16	It may be helpful to summarise these "novel risks" and "high levels of uncertainty" somewhere in the report (perhaps in a table), and compare them with relevant comparators (including systems). Moreover, this statement may not be applicable to all potential SynBio applications, so may benefit from being nuanced. Also the statement that these applications are challenging existing regulatory systems in an unprecedented fashion is very general and, as such, not supported by evidence.	Revision made.
United States of America	57	20-23	As currently written, this statement implies that existing risk assessment and management strategies across the board are not fit for use and need to be revised. We consider that stakeholders must also be provided essential information as to the benefits of the associated products/applications.	Comment noted.

			"However, the degree to which a risk is acceptable cannot be determined purely scientifically; science can predict the likelihood of certain effects, but non- scientific criteria must be included in the process of judging their acceptability (Johnson et al., 2007)."	
European Union	57	20-25	The flow of arguments is challenging to follow. Moreover, the authors may wish to expand on the fact risks/potential for harm can be assessed in a relative (comparative) manner (and thus against an acceptable baseline) or in an absolute manner. The report tends to focus on the absolute risks, without addressing relative risk assessments	Revision made.
Malaysia	57	28	Add the word "likelihood" to be consistent with text in Annex 3 of CPB ….could go wrong and how harm might occur (likelihood),	Editorial suggestion noted and revision made
European Union	57	30	Case. Add "case and its intended use"	Editorial suggestion noted and revision made.
European Union	57	38	Based in science, add "and based on scientific evidence that is available."	Editorial suggestion noted and revision made.
Malaysia	57	44, 45	"Suggestion to reword Risk assessment consideration for three synthetic biology supporting technologies that have received considerable regulatory attention to date are presented."	Editorial suggestion noted and revision made.
Canada	57	44, 45	Suggest the sentence be re-written as follows: "Some considerations regarding risk assessment for three synthetic biology supported technologies that have received considerable regulatory attention to date are presented below."	Editorial suggestion noted and revision made.
United States of America	57	44-45	We suggest the text edits in red below to reflect that risk assessments cover applications and not technologies. "~~Here b~~Below some considerations regarding risk assessment for applications of three synthetic biology supporting technologies that have received considerable regulatory attention to date are presented."	Editorial suggestion noted and revision made.
Belgium	57	46	A reference elaborating on plausible pathways for potential harm via problem formulation could be added: Connelly et al., (2021) Malaria J 20(1):170 - doi: 10.1186/s12936-021-03674-6	Editorial suggestion noted and revision made.

European Union	57	46	The quality of this section could be further improved.	Comment noted.
Malaysia	57	48	Add acronym. …for instance IAS and pests	Editorial suggestion noted and revision made.
Republic of Korea	57-60	46	This section fails to distinguish synthetic biology from conventional genetic engineering in terms of GMO development.	Until consensus is achieved concerning which techniques, processes or products will remain under the definition of genetic engineering and those that will now fall under synthetic biology, there will always be a divergence of views and opinions on this amongst the readers. The authors recognise therefore that a "blurring of the lines" between the 2 may occur at times, however it is not the place for this document to champion any particular distinction between them (see Section B. Scope and Mehtods).
European Union	58	09	Irreversibility is not applicable to all engineered gene drive applications, so this points needs to be nuanced. Moreover, irreversibility is likely to pose challenges for risk managers and decision makers but not necessarily risk assessors	Comment noted and revision made.
European Union	58	10-12	And what about spatial and temporal scale of spread of some gene drive modified organisms?	Comment noted and revision made.
European Union	58	16-17	It depends on the engineered gene drive systems so once again this statement should be nuanced	Comment noted and revision made.
United States of America	58	17-20	We suggest the text edits in red below to reflect that this evaluation was performed in context of EC guidance. "As such, EFSA noted~~they are concerned~~ that EC regulations regarding~~the~~ molecular characterisation, environmental risk assessment and post-market environmental monitoring specifically of gene drive-engineered insects are insufficient and thus want further guidance to be developed which builds upon existing approaches (Naegeli et al., 2020)."	Editorial suggestions noted and revision made.

European Union	58	20	Please correct the reference " Naegeli et al., 2020" as follows "EFSA GMO Panel, 2020"	Comment noted and revision made.
European Union	58	33-43	Once more, very general statements that may not be applicable to all potential engineered gene drive applications	Comment noted and revision made.
European Union	58	37	Models are not only used for prediction purposes, but also to better understand the system under assessment	Comment noted and revision made.
European Union	58	38	What about self-limiting/localised engineered gene drives?	Comment noted and revision made.
United States of America	58	38-42	We recommend enhancement of clarity as to how engineered gene drive-modified organisms cannot be limited in time and space. We note that particularly when used to suppress species populations, these gene drive applications are self- limiting and remove themselves from the population and this consideration should be included in the discussion. "Unlike non-engineered gene drive organisms which can be limited in time and space and therefore provide data from small-scale tests that can be relevant to large-scale releases, the potential of engineered gene drive organisms to spread over large areas and landscapes, even from a limited release or well-isolated trials, means that risk assessors will need to consider models and forecasts in their assessments."	Revision made.
European Union	58	42-43	This statement is too general to be helpful – further ecological work on what, and for what purpose?	Comment noted and revision made.
Argentina	58	45-49	The discussion about regulation of genome editing should not be part of the discussions on synthetic biology.	See scope and methods.
United States of America	58	47-49	We recommend more information be provided about this statement. It is not clear to us how this significantly differs from products developed using transgenic or other genetic engineering approaches and amending the text could add clarity. "The latter captures concerns about for instance, genome editing allowing for modifications that would not otherwise naturally arise (African Centre for Biodiversity, 2020; Kawall et al., 2020)i."	Revision made.

Malaysia	58	49	Remove “i”, unclear why the letter “i” is there Centre for Biodiversity, 2020; Kawall et al., 2020)i.	Editorial suggestion noted and revision made.
European Union	59	07-08	Proposed citation to add/consider: EFSA GMO panel scientific opinion on SynBio plants discusses the potential off target effect in genome edited synbio plants, based on case studies.	Editorial suggestion noted and revision made.
United States of America	59	09-10	We suggest the text edits in red below to reflect that the relevant techniques are genome editing techniques. “It’s been argued that the current approach to risk assessment is not designed to detect unintended consequences that arise from ~~of~~ employing some ~~new breading techniques (i.e~~ genome editing techniques (~~;~~ Christ et al., 2018).”	Editorial suggestion noted and revision made.
Canada	59	10	The word “breeding” was likely meant instead of “breading”.	Editorial suggestions noted and revisions made.
Belgium	59	10	"breeding" instead of "breading"	Editorial suggestions noted and revisions made.
United States of America	59	12-14	We recommend more information be provided about this statement. It is not clear to us what the criticism is that has been applied and amending the text could add clarity. “However, the use of untargeted metabolites in the characterization of these crops has also been subject of criticism (Court of Justice of the European Union, 2018; Lassoued et al. 2019; Marchant, 2001).”	Comment noted and revision made.
Argentina	59	13	Delete the reference to the Court of Justice of the European Union, 2018	Editorial suggestions noted and revisions made.
European Union	59	13	Reference to Court of Justice of the EU, 2018 is not related to the context.	Editorial suggestions noted and revisions made.
United States of America	59	21-24	We suggest more information be provided about this statement. It is not clear to us how this significantly differs from products developed using transgenic or other genetic engineering approaches and amending the text could add clarity. “Characteristics of some genome editing applications, e.g., the small extent of genomic sequence change and their higher targeting efficiency, i.e.,	Comment noted.

			precision, cannot be considered an indication of safety per se, especially in relation to novel traits (Eckerstorfer, Dolezel, et al., 2019)."	
European Union	59	25-41	Parties may also have specific guidance. Consider to add the references, differentiating the levels of data requirements.	Comment noted.
European Union	59	29	Add citation for EFSA GMO Panel opinion on SDN 1, 2 and ODM. Not in reference list or in the text	Editorial suggestion noted and revision made.
United States of America	59	48-49	We recommend clarification or deletion of the references to animal cloning methods. We note that currently, animal cloning predates and is not a genome editing technique. "However, a lack of scientific data on engineered animals, how animal systems respond to genome editing, mosaicism produced from animal cloning methods (e.g. somatic nuclear transfer)"	Editorial suggestion noted and revision made.
European Union	60	03	Only a fraction of relevant publications are cited – many more relevant papers (including more recent ones) have been published in the scientific literature	Comment noted.
European Union	60	07; Section 6.1.3	EFSA GMO panel has published in 2017 a guiding note on the assessment of RNAi off targets in plants and a review of it's activities (including several scientific opinions) on the risk assessment of GM plants based on RNAi. This recent work could be cited in this section, with reference to the EFSA scientific opinions for recently commercialized maize and soybean GM plants, as well as the external reports reviewing the state of the art for MC, FF, ERA (Paces 2017, Davalos 2019 and Christeans 2018)	Comment noted and revision made.
Argentina	60	11-12	Delete: "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." Many regulatory agencies have already assessed RNAi-based crops, and some of them are already in the field.	Comment noted and revision made.
Brazil	60	24	"In the meantime, Brazil, New Zealand, and Australia have approved RNAi-based GM plant events for environmental and food/feed	Editorial suggestion noted. Revision made.

			commercialisation without any changes or adaptations in their **case-by-case** risk assessment procedure **but with different risk hypothesis informed in data collected**"	
Malaysia	61	20	Add an example resistance to what. Just resistance lacks clarity.	Editorial suggestion noted and revision made.
Malaysia	61	23	Remove "and" at the end of the statement as this is not the penultimate point	Editorial suggestion noted and revision made.
Malaysia	61	24-25	No explanation is provided for this point, like the rest. Put ";and" at the end of the statement as this is the penultimate point in this list	Editorial suggestion noted and revision made.
European Union	61	29	Post-release/market environmental monitoring could be addressed as additional risk management strategy	Editorial suggestion noted and revision made.
Canada	62	08-20	The engineering of auxotrophic mutations is another approach to induce conditional lethality in bacterial cells by requiring the addition of a particular nutrient into the media to maintain viability. A good example of this approach is found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4579030/	Comment noted and revision made.
Canada	62	21	Suggest the title include the words "…for gene drives", as this section appears to focus exclusively on gene drives.	Editorial suggestion noted and revision made.
United States of America	64	08-10	We recommend clarification or deletion of this sentence. As described in the rest of the paragraph (lines 10-16), single nucleotide changes to the genome are unlikely to have unintended/off-target effects. Therefore, if the single nucleotide change could have been achieved through conventional breeding methods and would not be detectable, what is the need for detection and identification? We recommend inclusion of a stronger rationale or deletion of the sentence. "This has important repercussions for the effective detection and identification of synthetic organisms, and especially for those authorised for international trade (currently plant-based commodities)."	Comment noted.

United States of America	64	17-45	Referring back to the previous comment (pg 64, lines 8-10), we consider that this section does not give appropriate consideration to the notion that single nucleotide changes in genome-edited organisms are unlikely to pose a greater risk than their conventional counterparts and would thus not need to be subject to detection and identification processes. We suggest reframing this section to focus on the detection and identification of genome-edited organisms that require greater regulatory scrutiny than their conventional counterparts.	Comment noted and revision made.
Thailand	64	28-29	It is still unclear how we might distinguish between natural mutations that happen spontaneously vs mutation directed by genome editing (especially SDN-1).	Comment noted.
European Union	64	30-31	The potential of the method cited here is controversial. The European Network of GMO Laboratories (ENGL, 2/10/2020) concluded that "as the method thus does not allow to distinguish single nucleotide variants generated by genome editing from those obtained with classical breeding techniques or by natural mutation, it cannot be applied for unequivocal detection, identification and quantification". The ENGL also concluded that "additional validation work would be required to evaluate further the specificity, sensitivity and applicability of the method". We recommend to include these conclusions in the text.	Revision made.
European Union	64	36	We suggest to include an important conclusion of the European Network of GMO Laboratories, 2019: "Validation of an event-specific detection method and its implementation for market control is only feasible for genome-edited plant products carrying a known DNA alteration that has been shown to be unique	Comment noted, and revision made.
Republic of Korea	64	41-	The concept of "anticipatory framework" and the solution by "political will" are here suggested without much elaboration. In other words, do the current debates and concerns stem from the lack of this kind of framework and a certain political will? Perhaps rephrasing some sentences is needed to avoid any misunderstanding.	Comment noted.

European Union	66	15-16	The exemptions are not always treated as conventional products. Therefore, it would be more accurate to say that some countries treat the exemptions as conventional products while others apply specific conditions such as making a public consultation, publishing those decisions or introducing the exemptions in specific registers, requiring specific follow up or monitoring reports.	Comment noted and revision made.
Brazil	66	20-22	Delete the sentence from line 20 to line 22. The corn variety mentioned was not developed through synthetic biology. Genome edition in this case is similar to modifications achieved by conventional breeding or by spontaneous mutations. ~~"In 2018, Brazil ruled that Corteva's 'waxy corn' developed through the use of genome editing was not an LMO, thus exempting the product from biosafety regulations (Comissão Técnica Nacional de Biossegurança, 2018)".~~	Editorial suggestion noted and revision made.
United States of America	66	25-27	We note that this statement is inaccurate and we recommend that it be revised to reflect that the USDA has a narrow exemption that applies to single base-pair substitutions. Please refer to and reference https://www.aphis.usda.gov/brs/fedregister/BRS_2020518.pdf. "Further, the USA Department of Agriculture announced that it has no plans to place additional regulations on genome-edited plants that could otherwise have been developed through traditional breeding prior to commercialisation."	Comment noted and revision made.
South Africa	66	34-38	South Africa does not yet have a policy/guidance describing which genome-edited applications are not required to follow as indicated in the document. The decision-making body supported a scientific committee is considering different views from a experts and a range of stakeholders, including scientific experts, and reports such as "The Regulatory Implications Of New Breeding Techniques" developed by the Academy of Science of South Africa (ASSAf) (2016) to formulate a country position on how genome edited organisms will be regulated.	Comment noted and revision made.
European Union	66	38-40	The European Court of Justice ruled that organisms obtained by mutagenesis are GMOs as defined in EU legislation and that new	Comment noted.

			mutagenesis techniques are subject to the obligations of the EU GMOs legislation (Court of Justice of the European Union Case C-528/161). 1 Court of Justice of the European Union. (2018). Judgment Of the Court (Grand Chamber): Mutagenesis 40 — Directive 2001/18/EC, Interpretation and assessment of validity — Notion of 'genetically 41 modified organism' — Common catalogue of varieties of agricultural plant species — New 42 techniques of mutagenesis. http://curia.europa.eu/juris/documents.jsf?num=C-528/16#	
Canada	66	42-45	This does not appear to be supported by any statements expressed in the Ellens et al. 2019 paper. In the abstract of the paper it states: "…from a regulatory standpoint the Government of Canada views gene editing as another tool that will join current methods used to develop desirable traits in plants and animals. This is because Canada focusses on the potential risk resulting from the novelty of the trait, or plant or animal product entering the Canadian environment or market place, rather than the process or method by which it was created." Thus, it may be more accurate to say that plants, animals and their derived products (food, feed) produced through gene editing are regulated in Canada and subject to assessment based on whether novel traits are being expressed as a result of gene editing.	Editorial suggestion noted and revision made.
Brazil	66	45-47	~~"Likewise, Brazil's National Technical Biosafety Commission determined in 2018 that gene-edited hornless cows are conventional animals and that these cows and their products can enter the market (Genetic Literacy Project, 2020)".~~ The decision that concluded the gene edited hornless cows would not be a genetic modified organism (Technical Opinion Nº 6.125/2018) was cancelled in June 2019 (https://www.in.gov.br/web/dou/-/despacho-de-13-de-junho-de-2019-163601357).	Comment noted and revision made.
Malaysia	67	10	After the para on China, perhaps a statement can be added about the status gene editing regulation of CPB Parties in Asia. A general description, somewhat similar to what was mentioned for Africa (Line 48 Page 66). There is no mention of other Asian countries, other than China and Japan earlier on as a developed country (Line 34 Pg 66)	Comment noted and revision made.

Canada	67	11-12	It would be helpful to state who has put forward these arguments and cite a few sources.	Comment noted. Revision made.
United States of America	67	11-12	We recommend clarification and inclusion of a reference or deletion. It is not clear from the text who has suggested that greater difficulties in detectability abrogates a need for regulation. We note that limitations in detection are not sufficient to remove regulatory requirements, as it is a question of risk rather than detection. "It has been argued that the detectability of genome edited products is technically more difficult compared to GMOs, and that therefore there is no point in having them regulated."	Comment noted. Revision made.
Argentina	67	12	"…and that therefore there is no point in having them regulated", replace by "that because such products are similar to those obtained with conventional methods, the risks are also similar and therefore regulating them as GMOs may be disproportionate".	Comment noted. Revision made.
Canada	67	15-18	Suggest removing the last 2 sentences of this paragraph as they sound ambiguous and unfocused and do not appear to fit with the tone of the rest of the section.	Comment noted. Revision made.
United States of America	67	40-42	We suggest the text edits in red below to reflect that Parties can have their own flexible frameworks while staying within the objectives of the Protocol and that they must ensure that their processes follow their international agreements. "Therefore, Parties to the Protocol need to ensure an adequate level of protection in the field of the safe transfer, handling and use of LMOs ~~regulate such organisms according to the provisions of the Cartagena Protocol.~~"	Editorial suggestion noted and revision made.
Malaysia	68	40	Provide information on which section to refer to. Replace "later section" to the specific section being referred to. This has been done when cross references are made in other parts of this document.	Comment noted and revision made.

Canada	69	07-08	Synthetic biology in unnecessary quotations.	Comment noted and revision made.
Australia	69	15-17	The statement attributed to the Gene Technology Ethics and Community Consultative Committee (GTECCC) does not accurately reflect communiques of that committee and is not supported by the provided reference. The statement should be amended to reflect the published views of the committee and should be clearly identified as being in relation to applications existing in 2012, as follows: Australia's Gene Technology Ethics and Community Consultative Committee has stated that, as of 2012, known proposed applications of synthetic biology do not raise new ethical issues and would be regulated under the existing Australian legislation. This sentence should be supported by reference to the Gene Technology Ethics and Community Consultative Committee's May 2012 communique.	Comment noted and revision made.
Canada	70	07	Self-regulation in unnecessary quotations, as the term was defined and explained in the paragraph above.	Editorial suggestions noted and revisions made.
European Union	70	12	That that (remove repeated word)	Comment noted and revision made.
Canada	70	17	Formatting. Space required between "…2011)involving"	Editorial suggestions noted and revisions made.
Brazil	70	17-19	Delete from line 17 to line 19. Only peer reviewed literature should be used as a reference. ~~"After Asilomar, precautions for rDNA experiments gradually relaxed thereby laying the foundations for many of the technologies which underpin synthetic biology today. This relaxation has been attributed to the low incidence of accidents (Schmidt and Lorenzo 2010) and a "culture of safety" (Erickson et al., 2011) involving rDNA despite its increased use. Critics of self-regulation see the Asilomar Declaration as a strategic move to pre-empt greater government oversight and narrow the focus of concern (ETC Group, 2007)".~~	See scope and methods.
Canada	70	27	Formatting consistency. Elsewhere in the document, there is spacing between et al. and the bracketed year. In this line it is written as "et al.(2009)".	Editorial suggestion noted and revision made.

Brazil	70	46-47	Delete from line 46 to line 47. Only peer reviewed literature should be used as a reference. ~~"The ETC Group (2007), on the other hand, suggested that there was internal disagreement over whether or not to boycott non-compliant gene synthesis companies".~~	See scope and methods.
Republic of Korea	72	08-	It will be desirable to provide some examples of "Human Practices" done in i-GEM	Comment noted.
Malaysia	73	07-10	Break up these 2 statements. …..academic analysis. However, the challenges	Editorial suggestion noted and revision made.
Malaysia	73	24	Was it meant to be "this" instead of "his" ...scientists at this institute…..	Editorial suggestion noted and revision made.
Brazil	73	25-26	Delete from line 25 to line 28. Only peer reviewed literature should be used as a reference. ~~"Although ultimately abandoned, NGOs and commentators expressed concern at the breadth of its sweeping claims (Calvert, 2012; ETC Group, 2007, 2011) particularly in relation to creation of synthetic organisms for the production of biofuels like ethanol and hydrogen (van den Belt, 2013)".~~	See scope and methods.
Brazil	73	44-48	Delete from line 44 to line 48. Only peer reviewed literature should be used as a reference. ~~"In the USA, each patent application costs $10,000 (Henkel & Maurer, 2007). If patenting becomes established as the necessary method of claiming of IP rights on synthetic biology, the high cost could influence the kinds of applications of synthetic biology that are pursued (high profit applications targeting wealthy populations), as well as the types of organisations (continuing concentration of ownership and control in large transnational corporations) (ICSWGSB, 2011; ETC Group, 2007; Redford et al., 2013)".~~	See scope and methods.
Brazil	73, 74	50-51, 01	Delete the sentence from line 50 of page 73 to line 1 of page 74. Only peer reviewed literature should be used as a reference. ~~"A strong concern of civil society groups is that strong IP regimes could~~	See scope and methods.

			~~also restrict access to information for carrying out independent, effective risk assessments~~”.	
Malaysia	75	36	Remove the full stop (see Section 3.)	Editorial suggestions noted and revisions made.
South Africa	81	31	This section should appear earlier on in the document and summarised	Editorial suggestion noted.
Canada	81	41-42	Both SBSTTA and AHTEG are acronyms that have been previously spelled out, and therefore do not need to be spelled out again.	Editorial suggestions noted and revisions made.
Canada	83	23-28	Unclear as to why the phrase living modified organism is being put in quotation marks. The first instance may be quoting the Cartagena protocol, but the following instances are simply using the term.	Editorial suggestions noted.
Canada	84	03-24	Comment as above, why is the term living modified organism being placed in quotation marks. Additionally, consider either spelling out the phrase OR using the acronym LMO (after the first time) for consistency.	Editorial suggestions noted.
Malaysia	85	19, 20	Placement of parenthesis - remove parentheses before the word “such”. Add parentesis in front of Noyce. Remove parenthesis before “2018” …..natural organisms such as the reconstructed Horsepox virus (Noyce et al. 2018), karyotype engineered…..	Editorial suggestions noted and revisions made.
United States of America	87	24-40	We believe this paragraph could usefully note the outcomes from the 2020 Risk Assessment and Risk Management AHTEG, which indicated that additional guidance for LM fish is not necessary at this time.	Editorial suggestions noted. Revision made.
United States of America	88	21-23	We recommend including more information to explain why containment facilities for LMOs would be insufficient for organisms developed using SynBio. “First, the International Civil Society Working Group on Synthetic Biology (ICSWGSB) (2011) argues that containment facilities that Parties consider to effectively contain LMOs may be unsuitable to contain organisms resulting from synthetic biology techniques.”	Editorial suggestions noted and revision made.

United States of America	89	01-05	We recommend including more information to explain why the domestic release application would be insufficient to adequately assess and manage the risk from releasing an LMO. "A third and more general issue, which is not limited to LMOs produced by synthetic biology, is that Parties could be faced with "regulatory arbitrage" − the practice of utilising more favourable laws in a jurisdiction to circumvent regulation elsewhere − if a laboratory imports a synthetic biology LMO for contained use and then makes a domestic application to release the synthetic biology LMO from containment (ICSWGSB 2011)."	Editorial suggestion noted. Revision made.
South Africa	90	06	This section seems to be repeating information from the text of the Protocol without linking it to synthetic biology. Therefore, we propose deletion.	Editorial suggestion noted.
United States of America	90	32-34	We suggest the text edits in red below to reflect that this process is voluntary, using exact language from Article 26. "Article 26 of the Protocol addresses the extent to which Parties may take into account, consistent with their international obligations, ~~are entitled to take~~ socio- economic considerations ~~into account~~ in reaching a decision on imports of LMOs, including the value of biological diversity to IPLCs."	Editorial suggestions noted and revision made.
Thailand	94	30	A number of international rules, regulatory practices, processes and initiatives have emerged recently. It is confusing for general audience (including myself) to what extent these rules and regulations have been enforced and whether they have been in conflict with one another.	Comment noted. Revisions made.
Canada	96	27-29	Why is this sentence bolded? If quoting the WHO, place in quotation marks.	Editorial suggestions noted and revisions made.
Canada	101	06	Phrasing/Formatting. Consider either: "At its 17th meeting in 2016" or "At its 17th meeting (CoP17, 2016)".	Editorial suggestions noted and revisions made.
Canada	101	35	Formatting. Elsewhere in the document, instances of "th", "st", and "nd" following a number are superscript. In this line, it is written as "70th".	Editorial suggestions noted.

Canada	105	13	Formatting. If you abbreviate a name/term later, place the abbreviation in parentheses following the first time the phrase is used. In this case "The international Court of Justice (ICJ)" would be appropriate.	Editorial suggestions noted and revisions made.
European Union	107	46	Please correct the reference " Naegeli et al., 2020" as follows "EFSA GMO Panel, 2020"	Editorial suggestions noted and revisions made.
Cuba	108	44	into force in 1975 and currently has 168 Parties (Delete and substitute by 183) Today, the Convention has 183 States Parties – most of the world's countries As of 1 March 2021. See United Nations Office for Disarmament Affairs, Treaties Database, http://disarmament.un.org/treaties/t/bwc. and J. Revill, J. Borrie, R. Lennane and E. Saunders, 2021. "Preparing for Success at the Ninth Biological and Toxin Weapons Convention Review Conference: A Guide to the Issues", UNIDIR, Geneva. https://doi.org/10.37559/WMD/21/BWC/01.	Editorial suggestions noted and revisions made.
Argentina	108 [actually 106]	12-15	"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" Delete the whole phrase since there are not examples of synthetic biology.	Editorial suggestions noted and revisions made.
Cuba	110	37/38/39/40	Due to the Pandemic situation there is a new schedule: 1st Preparatory Committee (PrepCom) for the Ninth Review Conference of the Convention is scheduled for November 26, 2021 https://indico.un.org/event/35464/ 2nd Preparatory Committee (PrepCom) for the Ninth Review Conference of the Convention is scheduled for 4-8 April 2022. The Ninth Review Conference of the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (BWC) was originally scheduled for late 2021 and will take place in Geneva from 8-26 August	Editorial suggestions noted and revisions made.

			2022 at Palais des Nations https://indico.un.org/event/29589/	
Canada	111	20-21	Awkward phrasing. Consider "The Indigenous and Tribal Peoples Convention, 1989 (No. 169), also known as ILO-Convention 169, is an International Labour Organization Convention which as of March 2021 has been ratified by 23 countries."	Editorial suggestions noted and revisions made.
Cuba	121	32	…..leading to biosafety and biosecurity (addition) There are many biosecurity concerns (The issue of security) and some vulnerabilities that synthetic biology adds to them, misuse does not always require pathogen access (and biosecurity regulatory system is largely built on access control). On the Issue of safety (Biosafety Concerns) Contagious pathogen could spread beyond laboratory unintentionally as an accident, spread beyond borders and provoke an international incident. That's why the need of "a biosafety/biosecurity risk assessment as a systematic process of gathering and evaluating information to identify hazards, determine the associated risks and develop appropriate risk control strategies. For more specific information on how to conduct a risk assessment, please refer to section 2 risk assessment. Templates and additional guidance can also be found in Monograph: risk assessment and Monograph: biosafety programme management." (Laboratory biosafety manual, fourth edition and associated monographs) ISBN 978-92-4-001131-1 (electronic version)ISBN 978-92-4-001132-8 (print version) WHO, 2020.	Editorial suggestions noted. Revision made.
Cuba	121	35	…and plant health as well as the environment. This is an integrating approach "One Health" where several international, regional and national organizations are involve For Instance (WHO, FAO, OIE and CDC) in a human-animal-ecosystem interface. http://www.who.int/news-room/q-a-detail/one-health http://www.cdc.gov/onehealth/who-we-are/one-health-office-fact-sheet.html	Comment noted. Revision made.

United States of America	126	11-12	We suggest the text edits in red below to reflect that, although no international mechanism is currently in place, there is not an explicit need for one either "In this sense, what is immediately apparent from the international-level mapping described in Sections 8 and 9 is that no specific governance or process of rule-making on an international scale exists to 'regulate' synthetic biology, although the need for such a global mechanism has yet been determined."	Editorial suggestions noted.
United States of America	126	17-20	We suggested the text edits in red below. We consider that the rationale behind this statement is unclear. We note that the adoption of the term "synthetic biology", which is not defined, after the establishment of regulatory process does not necessitate that those processes require updating. Our suggested edits reflect that new tools have come into use and that there are new products/applications that may require updated regulatory mechanisms to assess. "In a similar manner, it is also important to consider that manyost regulatory mechanisms discussed in the present document were developed before some tools that enablethe term synthetic biology became widely used and therefore, they were not developed with the necessary scope and scale that some of the potential impacts of some applications of synthetic biology may present."	Editorial suggestions noted. Revision made.
United States of America	129 [actually 130]	02-04	We recommend including a reference to support this statement. "Social, economic, and cultural considerations are as equally important as the consideration of potential 2 impacts on biodiversity, conservation and sustainable use during decision-making and governance of 3 synthetic biology applications."	Editorial suggestions noted and revisions made.
Thailand	129	24-28	Some has predicted that synthetic biology will become more and more like information science, i.e., the cost and time required for building & testing biological systems will soon become irrelevant as the actual 'innovative' parts of the process are the learning and designing. Intellectual property frameworks previously used in the field of software engineering might	Observation noted.

			provide insightful lessons on how we shall manage IP in future synthetic biology.	
Republic of Korea	130	04-	It is true that relatively little "real world" data has been collected. I agree that, because of this situation, "any potential benefits of each application should, by necessity, be considered on a case-by-case basis." Yet, this paragraph does not really address the issues related to risk assessment. The lack of "real world" data is essentially the reason why CBD has embraced the precautionary principle in the first place. It is desirable to have a few sentences to deal with this point.	Comment noted.
Republic of Korea	131	13	Good examples of how civilian initiated projects can make a difference in dealing with the engagement issues. Perhaps the concept of "Global Observatory" on genome editing, suggested and pursued by a group of scholars, including Professor Sheila Jasanoff at Harvard Kennedy School, can be added to the list.	Revision made.
United States of America	131	27-29	We recommend providing more information as to why biosafety and biosecurity are complimentary approaches in this context. "Foremost, while the objectives are clearly different, it is evident that biosafety and biosecurity, at least in a containment context, are complimentary disciplines that benefit from an aligned approach."	Comment noted.
United States of America	131	36-38	We recommend providing a reference for the statement below. "The rapid advancement of the underlying science and the exponential rise in potential applications of synthetic biology is far exceeding the speed at which national and international governance frameworks can adapt."	Comment noted. Revision made.
South Africa	131	36-44	Regulation of Synthetic Biology at national levels should consider a synergistic approach between government and institutions, and alternatively a governance system that depend on an independent authority can be utilized especially for those products and/or technologies that do not fall within the scope of existing regulatory frameworks. Miller and Selgelid (2007) suggested this approach. Synthetic biology is also anticipated to increase the amount of genetically engineered organisms to be reviewed and the use of an independent	Comment noted.

			authority will also be useful to curb the influx and unburden the existing regulatory systems.	
United States of America	132	07-09	We recommend providing more detail and a stronger rationale for the statement below. It is not clear why and how engineered gene drive-modified organisms are an effective lens for viewing all synbio applications. "As synthetic biology applications approach commercial deployment and potential environmental release, engineered gene drives provide a useful lens through which to evaluate overlaps and potential gaps in the governance of synthetic biology."	Comment noted. Revision made.
United States of America	132	30-31	We recommend providing more information, especially for the opposing view. We consider that the following paragraph should not be predicated solely upon a single view. "There is a view that humans should not intervene in nature at all using a technology such as gene drive-modified organisms."	Comment noted.
Republic of Korea	132	31-	This kind of phrasing gene drive issues – the responsibility frame of doing it now or waiting it for later – is not persuasive. It looks too deterministic (following technological determinism) and too simplistic (without considering other options). It is important to acknowledge the complexity of this contentious issues and lay out as long as possible options.	Comment noted.
United States of America	132	43-44	We suggest the text edits in red below to remove the hyperbole and to place this in the appropriate context. "Since the publication of the previous technical series on synthetic biology in 2015, the number of synthetic biology applications has continued to greatly increase~~advance exponentially~~."	Editorial suggestions noted and revisions made.
United States of America	132	48-49	We recommend providing more detail regarding what clarity is being achieved. "As the field continues to advance and more applications become available, there is a growing pressure towards achieving clarity."	Revision made.

Brazil	133	08	"In contrast, a change since 2015 is the availability of commercial products for use directly in the environment, including genome edited soya bean, engineered bacteria fertilisers and self-limiting insects**, although due to the broad definition of synthetic biology adopted by CBD many of the products described are LMOs**".	Comment noted. There is not adoption of a definition, but an operational broad definition while a consensus is achieved.
Argentina	133	08	The self-limiting insects referred to are considered LMOs that are assessed under existing regulatory frameworks – it is not synthetic biology (field trials were performed before the 2015 synthetic biology technical series).	Until consensus is achieved concerning which techniques, processes or products will fall under synthetic biology, there will always be a divergence of views and opinions on this amongst the readers (see Section B. Scope and Methods).
United States of America	133	08-10	We recommend providing more information or deleting the statement below. We note that at present, there are no genome-edited animals or gene-drive modified organisms that are close to being released into the market. "Additional products intended for environmental release are in advanced stages of development, such as genome edited animals and organisms containing engineered gene drives to control vector-borne diseases."	Revision made.
United States of America	133	16-20	We suggest the text edits in red below as the rationale behind this statement is unclear. We note that the adoption of the term "synthetic biology", which is not defined, after the establishment of regulatory process does not necessitate that those processes require updating. Our suggested edits reflect that new tools have come into use and that there are new products/applications that may require updated regulatory mechanisms to assess. "It is also noteworthy to consider that many~~ost~~ ost regulatory mechanisms (i.e those discussed in the present document) were developed before the some tools that enable~~the term~~ synthetic biology became widely used, and therefore may not have sufficient oversight, in terms of scope and scale, for some of some applications of the potential impacts from synthetic biology.	Editorial suggestion noted. Text revised in response to previous (similar) comment.
United States of America	133	27-28	We recommend providing more information, as well as references, to "perceived need" in the statement below. "... there is also a perceived need for the development of additional tools to complement this and other existing methodologies."	Comment noted.

United States of America	133	28-30	We suggest the text edits in red below to reflect that not all applications of synthetic biology may require detection and identification, which could reduce strain. "Further, the inability to potentially detect and identify the applications of synthetic biology can add~~s~~ complexity and may strain the abilities of developing nations whose regulatory frameworks may not be (fully) developed, emphasizing the importance of focusing detection on applications that contain inherent risks."	Editorial suggestions noted. Revision made.
Canada	133	30	"Fully" does not need to be placed in parentheses.	Comment noted and revision made.
Brazil	133	35	"A common feature of articles identifying gaps or deficiencies in the governance of synthetic biology focus on the operation of 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 beyond human health and the environment to a more holistic approach that also encompasses social impact, ethical principles, and elements of social justice**, if required by national legislation as those elements can be part of decision-making**".	Comment noted.
Brazil	134	32-34	"To avoid unintended irreversible environmental damage and their associated geopolitical threats, ~~innovative research guidelines, governance methods, integration with social sciences~~ **capacity building, information and knowledge-sharing, technology transfer, risk assessors training, and integration with academia**, and engagement with communities are needed".	Revision made.
Brazil	134	39-43	"~~Calls for improved governance of synthetic biology, including addressing gaps in the international legal and regulatory frameworks, place significant emphasis on the need to better address societal, economic, and ethical dimensions. Enhanced regulatory oversight addressing these dimensions appears desirable to promote public trust and acceptance, however, the international laws, processes and initiatives analysed appear ill-equipped to address several of these dimensions~~".	Comment noted.

European Union	165	20-26	Please correct the reference as follows: "EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), Naegeli, H, Bresson, J-L, Dalmay, T, Dewhurst, IC, Epstein, MM, Guerche, P, Hejatko, J, Moreno, FJ, Mullins, E, Nogué, F, Rostoks, N, Sánchez Serrano, JJ, Savoini, G, Veromann, E, Veronesi, F, Bonsall, MB, Mumford, J, Wimmer, EA, Devos, Y, Paraskevopoulos, K and Firbank, LG, 2020. Scientific Opinion on the adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives. EFSA Journal 2020;18(11):6297, 90 pp. https://doi.org/10.2903/j.efsa.2020.6297"	Editorial suggestions noted and revisions made.
Belgium	167	44	Link is broken, please replace it with the correct link: https://www.biosafety.be/sites/default/files/120911_doc_synbio_sbb_final.pdf	Editorial suggestions noted and revisions made.

(*) "revisions made" refer to actions undertaken by the authors in an attempt to address the comments. The revisions may not necessarily incorporate all changes or specific text suggestions from reviewers.