Comments on the study on concept and scope – Organizations				
Organization	**Page #**	**Line #**	**Comment**	**Action taken and comments**
Expert committees of the German Research Foundation (DFG)	0	0	The fundamental problem with the document is the lack of a clear definition of synthetic biology (and other biological terms) and the incomprehensible mixing of different subjects and methods that do not really have anything to do with each other (from genome editing to classical genetic engineering to gene drives, all under the umbrella term of synthetic biology); see for example https://epsoweb.org/wp-content/uploads/2018/11/17_08_30_EPSO_Synthetic-Biology_updated-Statement.pdf Considering a genome-edited soybean, for example, that only carries a simple knockout mutation (permanent alteration of the genetic material through specifically making one or more genes inoperative), a product of synthetic biology is bold. The displacement of "natural" products by synthetic products has nothing to do with synthetic biology but is (if anything) a problem that is independent of the manufacturing process. For example, if vanillin is no longer produced from vanilla but chemically from wood, as is already predominantly the case, there are the same "problems" as if one were to use synthetic biology methods for vanillin production (e.g., key message 8 in the Executive Summary). In this respect, the document is fatally reminiscent of the demagogic argumentation on green genetic engineering, where there are still regular attempts to present general problems of agricultural production (monocultures, variety monopolies, etc.) as problems specific to genetic engineering. At the same time, it is hardly possible to assess how even small trait shifts in species communities in the field (natural or not) initiate community-assembly processes that potentially lead to species shift or biodiversity reduction. It is difficult to predict if and when genome editing will create a "super species". Such possible consequences of genome editing and classical mutation or mutagenesis breeding, but also of synthetic biology, should be taken seriously, and a roadmap for how to investigate ecological risks should be developed. Although there are cultivated species that disperse into semi-natural habitats and lead to the displacement of biotic communities, this has	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).

			not been sufficiently described in the literature so far or only for invasive alien species and too little in the agricultural context. Overall, therefore, a detailed specification of the different subjects mentioned at the beginning would be desirable, as well as a clear delineation of methods and modified organisms with specific risk assessment in each case. If the legislation continues to stick to method-related regulations and does not take the risk assessment of the intended modified organisms or biological entities as a decision criterion for specific applications, no progress can be made in the matter. As with the release of genetically modified organisms, a step-by-step approach – where possible – is certainly sensible. Otherwise, precise impact assessments must be carried out in the event of non-retrievability from nature. In the case of gene drive this is certainly relevant, but in the case of small point mutations, which could also occur spontaneously, rather not. All this ultimately leads to a document that is incoherent in itself and that, in its current form, can only accompany a critical discourse on synthetic biology but hardly serve as a basis for decision-making. In fact, the current situation of decision-making processes concerning synthetic biology and genome editing is very dynamic. In order to promote research and innovation, the CBD should revise the document to achieve a comprehensive text, including robust subject definitions and with an appropriate timeframe. These remarks are substantiated as follows (WC – row immediately below):	
Expert committees of the German Research Foundation (DFG)	0	0	The entire document suffers and loses credibility through the lack of a clear definition of what is considered synthetic biology. This leads to a confusion of synthetic biology applications with classical GMOs and with conventional genetic engineering. Overall, the document mostly ignores the fact that synthetic biology applications can overcome limitations of classical agriculture and GMOs with respect to invasiveness and potential harm. The rational design phase inherent to synthetic biology contributes to a tighter control over the product organism. It is possible to establish reliable containment strategies.	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

			In many passages the tone of the document implies that synthetic biology organisms would principally carry a higher risk than, for instance, introducing whatever non-GMO or GMO organism in each environment. It is hence not sensible to evaluate them on different grounds. The document misleadingly confuses gene editing with gene drives; the underlying agenda is apparently to discredit gene editing as a method. The apparent intention is to counter a regulatory approach that considers the product and not the process or means involved in generating such organism, for instance in regulatory frameworks for feedstock/foods (EFSA, USDA/FDA). If the product of an edited organism (plant) is not different (environmental risk, nutritional aspects) from a corresponding wild type, a naturally occurring or randomly induced mutant, or a conventionally bread organisms, then there are no scientific grounds for considering or regulating it differently.	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 as possible (see Section B. Scope and Methods).
EMBL	0	0	A: EMBL's Expertise. The European Molecular Biology Laboratory (EMBL) welcomes the opportunity to comment on this updated draft report on the CBD Technical Series on Synthetic Biology 82 (hereinafter "the Report".) . The EMBL is a molecular biology research institution supported by 27 member states, two prospect states, and one associate member state. It is Europe's only Intergovernmental Organisation for life science research. Innovative and interdisciplinary research at EMBL is conducted by more than 80 independent groups covering the spectrum of molecular biology. EMBL's overarching goal is to understand the molecular basis of life, and research at EMBL emphasises experimental and computational analyses of biological organisation, from molecules to organisms.Research areas cover a wide spectrum of biology, including structural biology, genome biology, cell biology, developmental biology, tissue and organ biology, neurobiology, microbiology, biodiversity, bioinformatics and computational biology, synthetic biology and molecular medicine. Adding to this, EMBL's vision is to advance our understanding of ecosystems at the molecular level, applying expertise in molecular biology to study life in its natural context. In doing so, EMBL aims to use fundamental science to tackle societal challenges,	Comment noted.

			including active consideration of bioethical and societal aspects of research pertaining to molecular biology in Europe. Research areas cover a wide spectrum of biology, including structural biology, genome biology, cell biology, developmental biology, tissue and organ biology, neurobiology, microbiology, biodiversity, bioinformatics and computational biology, synthetic biology and molecular medicine. Adding to this, EMBL's vision is to advance our understanding of ecosystems at the molecular level, applying expertise in molecular biology to study life in its natural context. In doing so, EMBL aims to use fundamental science to tackle societal challenges, including active consideration of bioethical and societal aspects of research pertaining to molecular biology in Europe. We believe that EMBL is, therefore, well placed to comment on the potential benefits and complexities of synthetic biology, as well as to respond to the conclusions and concerns raised in the Report. B: Comments on the Report Although we recognise that the Report outlines both positive and negative perspectives on synthetic biology, we are of the opinion that the general tone and scope could end up setting a dangerous precedent of restrictive legislation across the board, which would ultimately impede scientific research and development of societal importance. The following summary outlines our concerns in more detail. 1. It is our view that although the majority of synthetic biology applications currently stem from engineering microbes (something that took place long before synthetic biology was even invented, and is quite well regulated – both points acknowledged in the Report), the Report instead mainly focuses on the danger / risks regarding gene drives and / or animals only. While we acknowledge the need for discussion on topics such as Gene Drive, this is at odds with the Report's proposal that there is a need for a unified framework that regulates all elements of synthetic biology. 2. The Report argues for "a process and expected outcomes that better align with the needs and values of society more broadly than human health and the environment", such as "societal and ethical issues" and including economic factors. Again, it is concerning that this is the argument given for the need for new mechanisms across the board, despite the fact that all obvious 'risks'	

			cited concern mostly human and environmental health. 3. We believe there is an important nuance that has been omitted re microbes in the Report. For microbes, exchange of genetic material across species is rampant and happens naturally (in much more imaginative ways than genetic engineering and synthetic biology have proposed). Hence, one of the most efficient ways to obtain microbes with specific traits is to undertake experimental evolution rather than genetic engineering/synthetic biology, and this would only increase with the use of microbial communities. We propose that this perspective is taken into account in the report for completeness. C: Recommendations We oppose the recommendation for implementing umbrella frameworks, unless and until leading molecular biology institutes (such as EMBL) have been both involved in and informed of their creation. We believe that issues of bioethics and biosafety are important concerns in which scientists must engage, to help build monitoring frameworks or processes which are transparent and easily measured. Experimental approaches, and material/data reuse cannot always be proscribed: regulations must remain flexible in this area. Exchange of materials between labs (samples, organisms, genetic material) and data derived from those materials is essential to science, interactions and sharing must be smooth and friction must be low. We advocate the principles of Open Science - accessible to all and of benefit to all - and believe that access and Benefit Sharing systems are crucial, and must in turn be harnessed to support Open Science. The current pandemic has illustrated the need for rapid, open scientific exchange of data, knowledge and expertise. We fear that the report will lead to measures that will slow down or even paralyse certain areas of critical scientific practice and research. The value of some synthetic biology approaches as tools to explore and understand biological systems, from the molecular scale to whole ecosystems must be underlined. Access to synthetic biology in combination with traditional approaches will better and more rapidly allow the scientific community to describe living systems and to understand the complexities of biodiversity, including its origins and vulnerabilities, how best it might be	

			sustained and conserved and how its value might be brought responsibly and sustainably to society. It is, therefore, an important driver of the science upon which the Convention on Biological Diversity must build its actions. We, therefore, strongly recommend that there should be further consultation with molecular biology institutes like EMBL (and others, such as the European Synthetic Biology Society) before the draft proceeds to a final report. We believe that this would help remedy the identified inconsistencies, and allow for a more nuanced perspective on the issue. We would be happy to provide further input as required.	
German Joint Study Group on Synthetic Biology (GJSG on SynBio) of: Society for Chemical Engineering and Biotechnology (DECHEMA), German Botanical Society (DBG), Society for Biochemistry and Molecular Biology (GBM), and German Chemical Society (GDCh)	0	0	The entire document suffers and loses credibility through the lack of a clear definition of what is considered synthetic biology. This leads to a confusion of synthetic biology applications with classical GMOs and with conventional genetic engineering. Overall, the document mostly ignores the fact that synthetic biology applications can overcome limitations of classical agriculture and GMOs with respect to invasiveness and potential harm. The rational design phase inherent to synthetic biology contributes to a tighter control over the product organism. It is possible to establish reliable containment strategies. In many passages the tone of the document implies that synthetic biology organisms would principally carry a higher risk than, for instance, introducing whatever non-GMO or GMO organism in each environment. It is hence not sensible to evaluate them on different grounds. The document misleadingly confuses gene editing with gene drives; the underlying agenda is apparently to discredit gene editing as a method. The apparent intention is to counter a regulatory approach that considers the product and not the process or means involved in generating such organism, for instance in regulatory frameworks for feedstock/foods (EFSA, USDA/FDA). If the product of an edited organism (plant) is not different (environmental risk, nutritional aspects) from a corresponding wild type, naturally occurring or randomly induced mutants, or a conventionally bread organisms, then there are no scientific grounds for considering or regulating it differently.	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).

Helmholtz Assn	0	0	General comment: Statement from the Research Field Health of the Helmholtz Association of German Research Centers (Helmholtz Assn) Re: Convention of Biological Diversity (CBD) Notification 2021-031. Draft Update of the „CBD Technical Series No. 82“ on Synthetic Biology The Helmholtz Association is Germany’s largest research organization substantially supporting biomedical research in its research programs within the Research Field Health and its participating centers: Cancer Research at German Cancer Research Center (DKFZ) and Helmholtz-Zentrum Dresden-Rossendorf (HZDR), Environmental And Metabolic Health at Helmholtz Zentrum Munich (HMGU), Systems Medicine and Cardiovascular Diseases at Max Delbrück Center for Molecular Medicine (MDC), Infection Research at Helmholtz Center for Infection Research (HZI) and Neurodegenerative Diseases at German Center for Neurodegenerative Diseases (DZNE). The Helmholtz Health Centers have helped to develop some of the tools described in the CBD report on Systems Biology, and routinely deploy them to improve human health and well-being. As scientists routinely using the genetic engineering tools outlined in this report on synthetic biology, we are aware of our obligation to ensure that research is used safely for the benefit of humanity. A key value we share with the CBD is to ensure that our research is performed ethically and safely, while minimizing its impact on the environment. In all of our research institutes, significant regulatory infrastructures have long existed to ensure that our work is performed to minimize its potential for impacting the environment and biodiversity. For instance, in response to concerns on genetically engineered organisms and their potential impact on the environment if released, we have in place stringent internal licensing structures for performing any research involving genetically modified organisms (GMOs). To this end, we have dedicated Biosafety offices that advise and mediate between the overseeing governmental authorities and research scientists. Our experience in undertaking biomedical research has convinced us that an open and flexible approach towards scientific research results in the best outcome for society and for the environment. Open science includes	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). Revisions made.

			principles where proscriptions on specific protocols only exist when clearly necessary due to specific identified risks, where the re-useability of research results is encouraged to maximize societal benefit, and where the exchange of biological samples and reagents is encouraged. Blanket regulations which may impact these principles should be slowly considered and undertaken, with all stakeholders including the researchers themselves consulted carefully and repeatedly. Especially, internationally binding treaty restrictions must be carefully balanced between scientific risks and rewards, as there is considerable risk of damaging the benefits deriving from research. Regarding the current draft, we have concerns regarding the intention, structure, and conclusions of the circulated draft. Most prominently, the scope and definition of synthetic biology in this document is not well defined, as the authors themselves state (P8L9-12). There is a lack of clarity regarding what techniques and organisms should be considered synthetic biology, and why. Many of the examples described are already controlled closely as they are GMOs or techniques for creating such (CRISPR-cas9), for which there are considerable regulations already in place legally and within our institutions. It will be imperative for any revised draft to clearly delineate how their definition of synthetic biology differs from GMOs, and why it will require additional controls. We welcome an informed discussion on the societal and environmental impacts of recent developments in genetics, genomics, and synthetic biology. Here, however, we are concerned that a lack of definitional clarity has resulted in a list of techniques of interest to the CBD that is so broad it covers aspects of almost any modern biomedical research effort. Enacting binding restrictions on even a subset of these techniques could significantly impact our efforts to combat human disease.	
J. Craig Venter Institute (JCVI)	0	0	The 2021 draft of the Technical Series on Synthetic Biology is a welcome update to the original edition issued six years earlier. The draft covers an impressive number and breadth of publications on the topic. I have a few general suggestions for improvement before a final version is issued. First, the more detailed sections, i.e., Sections C, D, and E illustrate well the wide range of potential applications of synthetic biology, the breadth of the	Revision made.

			technologies, and hence the significant governance mechanisms that currently exist. However, the Executive Summary (Section A) and Conclusions (Section F) all too often state generalizations that are just too broad to be accurate for many, and in some cases, most situations. I appreciate the need for brevity in these sections, but this should not be at the expense of accuracy. Given that most readers will only read these summary sections, fewer generalizations and greater specificity will give readers a better understanding of the issues. Second, Section E (Governance) covers international governance in far greater detail than national and self-governance (50 pages vs 6 pages). Unfortunately, this does not give the reader a firm foundation from which to judge gaps and overlaps in overall governance and thus what is needed from international governance. A discussion of how these governance arrangements fit together would be very helpful. Third, the document covers the risk from applications of synthetic biology in greater depth than the benefits. Though only indicative, a quick search reveals the term risk appears 398 times in the document; the term benefit appears 206 times. Risks of synthetic biology applications are often presented without an explanation of the risks and harms the problems they hope to solve or from the technologies they hope to replace. Providing additional context from risk-risk and risk-benefit perspectives would be helpful when specific applications are discussed.	
UK Engineering Biology Leadership Council (UK EBLC)	0	0	The comments submitted herein represent the views gathered from leading practitioners of synthetic biology in the UK supporting the work of the Leadership Council and presented here on behalf of the UK Engineering Biology Leadership Council. As such, they represent views sometimes expressed in terms of 'I' or 'we' that we consider particularly important to be considered within this consultation. The advisory nature of the Leadership Council is such that they do not necessarily represent the formal views of any particular constituency represented within the Council. This report was commissioned to 'consider the potential positive and negative impacts …of synthetic biology' (p1 line 9). However, the report largely fails to consider the potential positive impacts and does not address the	Comment noted.

			opportunity cost of doing nothing. Indeed, this is conspicuously absent from the entire report. Our world is in crisis and the biggest threat is climate change driven by our fossil fuel based economy. Synthetic biology is one of very few technologies that has the potential to create a meaningful and positive impact. A transition to a bio-based economy should be an enormous impetus and driving force for this report, since this alone will have the most positive outcome for biodiversity and sustainability on our planet. There is an insufficient balance of risk and benefit with undue focus on risk, without due consideration of the risk associated with current approaches i.e. of doing nothing. The report ignores the fact that synthetic biology does not exist in a technological vacuum. Many aspects of human behaviour drive biological evolution and change. For instance the use of antibiotics has driven the increase of antibiotic resistance to the extent that it now constitutes an enormous threat to human health. However, antibiotics have been second only to vaccines in saving lives and improving healthcare and I have never heard anyone suggest that they should never have been used because there might one day be resistance. Yet, this report seeks to limit the use of technologies with huge potential, not just for humankind, but for our planetary ecosystem. When considering and evaluating risk, we need to look more carefully at the modes and consequences of failure. Gene drives represent a radical new approach to combating insect borne diseases and pests. The fact that they actively propagate a genetic trait through a population is a radical change in genetic engineering. Yet we also know that these gene drives are very specific for their host populations, there is no viable mechanism of escape to other organisms. Citing the risk of off-target mutation is ridiculous given the acceptance of non-specific radiation and chemical based mutation methods. We also have good understanding of how gene drives break, their specificity means that they are susceptible to mutational escape. But these broken gene drives do not represent a risk. They can no longer force their spread through the population and their presence declines naturally. Indeed, our own genomes are full of broken transposable elements – natural mobile elements of DNA that can no longer move around, nature's own gene drive failures.	

			Case-by-case risk assessment is important, but do not overstate the case of the 'uniqueness' of synthetic biology.	
University of Puerto Rico-Rio Piedras	0	0	Peer Review of First Draft of "Updated CBD Technical Series 82 Synthetic Biology" (cc) 2021 Joseph Henry Vogel In Notification SCBD/CPU/DC/WM/MAQ/MW/8958, the Secretariat calls for peer reviews of the First Draft of the "Updated CBD Technical Series 82 on Synthetic Biology", hereafter the "Draft Report". The call restricts the format to a three-column template even though narrative better elicits the desired "focus on substantive matters rather than on editorial issues". In the columns to the left, to what page and line in the Draft Report should this paragraph be ascribed? I will answer my own question: page 0 line 0. This and the paragraphs to follow will be one long General Comment. Elision is deliberate omission. Absent from the 183-page Draft Report are three issues: regulatory capture, mandatory financial security and bounded openness over natural information. Inasmuch as all three greatly concern the implications of the Convention on Biological Diversity (CBD) and Nagoya Protocol (NP) for Synthetic Biology (Synbio), any continued absence in the revised report would be purposeful. Addressing regulatory capture, mandatory financial security and bounded openness requires formal economics, which is applied in the parallel Draft Study on "Article 10 of the Nagoya - Kuala Lumpur Supplementary Protocol on Liability and Redress and decision CP-9/15", hereafter the "Draft Study on NKLSP". Thus two closely related texts are now being vetted, with deadlines of 15 and 26 June 2021. The corresponding sets of peer reviews risk being "silo-ed", which is also the criticism of international regimes in the Conclusion of the Draft Report (p. 133). The sets should be integrated. This review of the Draft Report will integrate not only with that forthcoming of the Draft Study but also with previous reviews of the five commissioned studies on DSI and that of the study on transboundary situations [1]. When the studies and reviews are removed from the silos, the foundational flaws of the CBD and NP become evident and cross-cutting.	Comments noted. For this document, the operational definition of synthetic biology is given in Part B. Scope and Methods.

			Regulatory Capture A literature exists on "regulatory capture" for which George Stigler was awarded a Nobel Memorial Prize in 1982. The term is almost self-explanatory: industry commandeers policymaking against the public interest. Stigler's contribution coheres with the political philosophy for which his academic affiliation is eponymous: The Chicago School [2]. Among its advocates was fellow Nobelist Frederich August von Hayek, whose ideology complemented Stigler's aversion to an expansive State. According to Hayek, the State lacks the capacity to process the torrent of information necessary for efficient regulation. Attempts to do so usurp market-based solutions and put society on "The Road to Serfdom" [3]. The Draft Report is replete with statistics which would support the Chicago-School critique. "By 2017 more than 25,000 authors at 3700 organisations located in 79 countries had contributed to the synthetic biology research..." (p.10). Among those research streams will be high-impact-low-probability (HILP) events. But just how high is the high impact? And how low is low probability? And what is the landscape of events? Answers would be contentious. The Draft Report speaks of the need for regulation to be "future-proof", as unanticipated developments will raise new issues that may eclipse those still being discussed by regulators (p. 12). Mandatory Financial Security The knowledge necessary to allow or prohibit Synbio endeavors requires a mechanism of control, be it enabled by the operators, the market or the State. The Draft Report treats liability and risk assessment extensively, but does not discuss mechanisms of financial security, which is discussed in the Draft Study on the NKLSP. Mechanisms include compulsory insurance, risk-sharing, risk-pooling, compensation funds, bonds and self-insurance (aka "going naked"). Because compulsory insurance would put the kibosh on a large swath of Synbio, lobbying will undoubtedly accompany investment in R&D [4]. The history of nuclear energy policy in the USA merits review [5]. Through regulatory capture, liability could be capped for worst-case scenarios. The capping shifts the costs of HILP events to society whenever the damages	

			exceed the cap. A caveat is in order: uninsurable activities do not necessarily mean that the expected losses are greater than the discounted value of the premia paid. Risk assessment is a "public good" in the economic sense [6]. An efficiency argument can be made that the modeling of events be government-financed and placed in the public domain. Insurance ambiguity would thus be diminished and render economic many otherwise uninsurable activities. Is therefore compulsory insurance with government-financed risk assessment the solution to the HILP events of Synbio? The answer is nuanced. Cognitive biases in personal risk assessment are common to all cultures. People tend to confuse the low probability of an event as if the expectation were also low (probability multiplied by the value of the event). The analysis of such uneconomic behavior earned the psychologist Daniel Kahneman the 2002 Nobel Memorial Prize in Economics. Non- rational patterns of risk perception justify seat belt laws, prohibitions of construction in floodplains, lugubrious images on cigarettes packages and so on. Insurers are not inanimate conglomerations. They are composed of people who may sort out in dominance hierarchies, where cognitive biases are amplified, almost invariably from top to bottom. One suspects that non-rational decisions will also afflict insurers and re- insurers, albeit much less so due to corporate checks and balances. So, the societal problem is not that some Synbio activities will be uninsurable, but that they will be mistakenly insured. Should HILP events be uncapped and even one insurer liberally underwrite HILP events à la Hayek, liability would be limited through the insolvency of the insurer or re- insurer. Worries about regulations not being "future-proof" pale against those about an insurer being "judgement-proof". The State must intervene to impede the gung-ho insurer who, at the right price, never says "no". In other words, compulsory insurance cannot stand alone as the mechanism of control due to HILP events that hazard global catastrophes. This is one of many places where the State must "draw the line", to use Keynes's metaphor in response to Hayek's unbound enthusiasm for market-based solutions [7]. Compulsory insurance is thus a very large part of the solution, but not the whole solution. How did this issue not merit inclusion in the laboriously	

			constructed Draft Report? Had economists been among the authors, perhaps they would have suggested "regulatory capture", which assumes that they themselves were not captured. A biographical sketch of the authors is essential within the Draft Report. In the 2017 Report, 44 members were identified and in the 2019 Report, some 38 [8]. Has the composition changed again? What was the contribution of each co-author? Such disclosure is now common practice in multi-authored scientific publications. Compulsory Insurance and Grey Goo Risk assessment may bog down regulation for Synbio products that present no possibility of an HILP event. One imagines that the insurance premia for "cultured leather products" (p. 37) or "digital information storage using DNA molecules" (p. 39) could be easily incorporated into the cost structure of a firm. One sincerely hopes that this is also not true of engineered bacteria for "carbon recycling" (p. 35) with its attendant possibilities for the grey-goo scenarios of sci-fi. Because grey-goo is an existential threat, the Keynesian line should be drawn on all such applications of engineered gene drives. The question of intentions must also be asked: What for? Do we risk global catastrophe to clean up an oil spill, knowing that the contaminants will eventually disperse? Do we risk it to sequester carbon, knowing that cost-effective alternatives go unexploited (e.g., subsidizing a vegetarian diet, public transport, re-forestation)? Other than nuclear war, only Synbio portends a man-made doomsday within our lifetimes. And like the nuclear threat, the possibility is so awful that the public prefers not to think about it. Cognitive dissonance is real. The wisdom of the Russell-Einstein Manifesto of 1955 seems apropos "All, equally, are in peril, and, if the peril is understood, there is hope that [all groups] may collectively avert it" [9]. The nonchalance of the Draft Report about gene drives morphs into hubris: "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. However, as the development of	

			engineered gene drive organisms near potential release, further ecological work will be essential to enhance model predictions (Sánchez et al., 2020)" (p. 58). G-d help us. Bounded Openness over Natural Information Although the economics of uncertainty is not my area of specialization, the elisions of the Draft Report were sufficiently flagrant that even a non-specialist like myself could identify them. I will now focus where I can profess specialization: "access to genetic resources" and the "fair and equitable sharing of benefits arising from utilization" (ABS). Variance is as bedrock to economics as it is to biology. Just as risks vary across the landscape of Synbio, so too should the obligations for ABS. Many "BioBlocks" of Synbio have appeared in the published literature since the onset of molecular biology and others have been published in patents, long since expired. User resistance to any ABS obligation inheres to the perception of an ersatz clawback by Providers, who would be well advised to abandon such attempts. Common ground in ABS should be sought for genetic material not previously utilized in intellectual property. The definition of the term "genetic material" in the CBD and NP employs "material" without defining what is "material". The AHTEG operational definition of Synbio does likewise: “[S]ynthetic 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” (Decision XIII/17) (p. 8). Most Users insist that "material" be interpreted as only tangible for the purposes of ABS. Do they also interpret "material" as only tangible in the operational definition of Synbio? If their interpretation shifts between the "silos" for ABS and biosafety, then good faith comes into question. If their interpretation does not shift, then the definition of Synbio loses all operability. "Genetic material" interpreted as only tangible suppresses the role of some 1700+ databases worldwide in the phenomenon defined. A literature exists that resolves the contradiction by distinguishing natural from artificial information and rejecting the placeholder "digital sequence	

			information" [10]. In reductionist terms, the object of access is natural information and any value added through R&D, artificial information [11]. The medium of natural information may take various forms for which the tangible (biological samples) and the digital are currently the most prevalent. The Sociedad Peruana de Derecho Ambiental (SPDA, Peruvian Society of Environmental Law) has suggested the following definition for Synbio, which is both broad and discriminating, while affording exclusionary criteria: Synthetic Biology: the extremely intensive use of artificial information in the manipulation of natural information [12]. One indicator of the intensity of artificial information would be extensive use of patented inventions [13]. Equal treatment of natural and artificial information implies that both enter the public domain when a patent expires. Should a commercial application arise that enjoys intellectual property protection for which the utilized natural information is not public domain, then equal treatment would mean that economic rents be shared among the countries of origin through a Global Multilateral Benefit-Sharing Mechanism (GMBSM), which is the title of Article 10 of the NP. The rents would vary by the class of utilization. Classification of certain endeavors as Synbio would thus facilitate negotiation of a royalty rate for that class [14]. The scant 50 lines on pages 92 and 93 (Sections 8.4 and 8.4.1) about ABS and the NP make no reference to this literature. The absence of any mention of the GMBSM speaks loudly. Conclusion. The narrative of this General Comment addresses the call to "focus on substantive matters rather than on editorial issues". The obligatory template biases peer reviews against identifying elisions. This peer review recommends that authors address substantively three issues: regulatory capture, mandatory financial mechanisms and bounded openness over natural information. A significant literature exists which throws light on the implications of the CBD and NP for Synbio, however the field is ultimately defined. [1] For my peer reviews of the four inter-sessional studies on DSI in 2018-	

			2020, see https:// www.cbd.int/abs/DSI-peer/2019/Study1/JosephHenryVogel.pdf, https://www.cbd.int/abs/DSI-peer/2019/Study4/JosephHenryVogel.pdf, https://www.cbd.int/abs/DSI-peer/2019/Study2-3/ JosephHenryVogel.pdf. Peer review of the antecedent 2017 study on DSI can be found at https://www.cbd.int/abs/DSI-peer/Vogel,%20UPR.pdf, and that of the 2020 study on transboundary situations, at https://www.cbd.int/abs/Art-10/Peer-review/Vogel.pdf. [2] See Filppo Maria Lancieri and Luigi Zingales, "Economic Regulation after George Stigler",, ProMarket: Publication of The Stigler Center at the University of Chicago, 2021. https:// promarket.org/2021/04/14/economic-regulation-after-george-stigler/. [3] F.A. Hayek, The Road to Serfdom, Chicago: University of Chicago Press, 1944. [4] Expenditure on lobbying is unconstrained in the non-Party, under Citizens United v. Federal Election Commission, 558 U.S. 310 (2010). [5] Garrett Hardin critiqued mid-twentieth century nuclear-energy policy with insights that are eerily prescient for twenty-first century Synbio. See his capstone oeuvre Living Within Limits, New York: Oxford, 1993. [6] "A good that is non-excludible and non-depletable (non-rivalrous)". Brittanica. https:// www.britannica.com/topic/public-good-economics [7] J.M. Keynes, 'Letter to Hayek' (28 June 1944) in Vol. 27 of the Collected Writings of John Maynard Keynes (ed.), Donald Moggridge, London, 1980, p. 385. [8] See, https://www.cbd.int/doc/c/aa10/9160/6c3fcedf265dbee686715016/synbio- a h t e g - 2 0 1 7 - 0 1 - 0 3 - e n . p d f a n d h t t p s : / / w w w. c b d . i n t / d o c / c / 2 0 7 4 / 2 6 e 7 / a135b1b57dabe8e8ed669324/synbio-ahteg-2019-01-03-en.pdf [9] "The Russell-Einstein Manifesto", issued in London, 9 July 1955, http://umich.edu/ ~pugwash/Manifesto.html [10] See trilogy of OP-EDs and references therein, published open-access in several languages from Intellectual Property Watch: "Ending Unauthorised Access to Genetic Resources (aka Biopiracy): Bounded Openness", 6 April	

			2018, http://www.ip-watch.org/2018/04/06/ending- unauthorised-access-genetic-resources-aka-biopiracy-bounded-openness/ , “Not Just A Matter Of Matter: ‘The Way Forward’ For The UNCBD, NP And Half-Earth”, 7 September 2018, http://www.ip-watch.org/2018/09/07/not-just-matter-matter-way-forward-uncbd-np-half-earth/ , “The Global Multilateral Benefit-sharing Mechanism: Where will be the Bretton Woods of the 21st Century?”, 5 October 2018, http://www.ip-watch.org/2018/10/05/global-multilateral-benefit-sharing-mechanism-will-bretton-woods-21st-century/ [11] See Genetic Resources as Natural Information: Implications for the Convention on Biological Diversity and Nagoya Protocol, Manuel Ruiz Muller, London, Routledge, 2015. Spanish translation, 2nd edition, in open access at https://spda.org.pe/?wpfb_dl=4131 [12] Sociedad Peruana de Derecho Ambiental ‘Submitted view for the Updated report and synthesis of views in response to paragraph 7(b) of Decision XII/24; and Report of the Meeting of the Ad Hoc Technical Expert Group on Synthetic Biology’, http://bch.cbd.int/synbio/peer- review/2015-2016/ [13] "One early example [of Synbio] is genetically modified ‘golden rice'—actually developed before the term synthetic biology was widely used—for which more than 70 patent rights needed to be cleared". Berhold Rutz, "Synthetic biology and patents. A European perspective", EMBO Reports 2009 Aug; 10 (Suppl 1): S14–S17. https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC2726002/#b13 [14] Joseph Henry Vogel, Klaus Angerer, Manuel Ruiz Muller and Omar Oduardo-Sierra, “Bounded Openness as the Global Multilateral Benefit-Sharing Mechanism for the Nagoya Protocol”. Pages 377-394 in Charles R. McManis and Burton Ong (eds) Routledge Handbook on Biodiversity and the Law, London, Routledge, 2018.	
Western Michigan University	0	0	The broad working definition of synthetic biology adopted by the CBD creates a difficulty for this document, since there are examples of synthetic biology mentioned herein that are inappropriate, since they would be products of methods that predate LMOs. Therefore, this document illustrates the lack	Until consensus is achieved concerning which techniques, processes or products will remain under the definition of genetic engineering and those

			of clarity regarding the term that underpins all the current discussions of synthetic biology under the CBD.	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).
Western Michigan University	0	0	As a related comment, the confusion about whether synthetic biology is a single discipline, which it is not in this reviewer's opinion, or a collection (yet to be defined) of disciplines pervades this document.	Revisions made.
Western Michigan University	0	0	The status of certain projects mentioned in this document should be re-evaluated, since, for example, characterizing gene drive containing solutions for public health as in advanced development is inaccurate.	Revisions made.
International Seed Federation (ISF)	0	0	The International Seed Federation (ISF) is a non-governmental, non-profit organization. ISF represents more than 7500 seed companies active in breeding, seed production and trading and is widely regarded as the voice of the global seed industry. One of the primary objectives of ISF is to facilitate the movement of seed within a framework of fair and science-based regulations, whilst serving the interests of farmers, growers, industry and consumers. ISF believes that the adoption of science-based, consistent policies for products of the latest plant breeding methods, will facilitate the development and uptake of advanced, innovative breeding applications by private and public breeders in developed and developing countries. ISF welcomes the opportunity to provide comments on the draft update of the CBD Technical Series No. 82 document entitled "Synthetic Biology". ISF	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 two may occur at times,

			notes that through decision 14/19 the Conference of the Parties requested an update of the previous document resulting in the significantly expanded and extensive document presented for peer review. The title of the document suggests that the Technical Series No. 82 is limited in scope to developments in synthetic biology. However, because of the broad interpretation by the authors of the definition of synthetic biology under the CBD, the document covers not only synthetic biology but any developments in biotechnology in general. For example, the authors extensively collect and present information on simple applications of genome editing techniques that result in genetic changes (mutations) that could also occur through processes in nature or by conventional breeding methods. Authors should not incorrectly invoke the impression that applying genome editing techniques per se results in synthetic biology or is synthetic biology. Genome editing techniques can be applied in a wide array of protocols and are merely enabling technologies. A differentiated evaluation of the outcome of the application of any method in biotechnology needs be undertaken as to whether the result would qualify as an organism obtained through synthetic biology. In this regard ISF opposes the generalized view on methods of biotechnology as methods of synthetic biology as done by the authors in general and the singling out of genome editing methods in particular. In the following we provide specific comments on particular passages of the text where revision in this regard is necessary. Still, the text needs to be carefully and thoroughly revised throughout to ensure that only examples truly representing synthetic biology examples are considered and not biotechnology as a whole. Otherwise the content of the Technical Series No. 82 will not correctly reflect its title "Synthetic Biology" but rather is an update on recent developments in biotechnology in general. Moreover, the document would greatly benefit from a summarized register of chapters that have been updated or added compared to the previous document from 2015. We understand that the draft update of the Technical Series No. 82, while still being under peer review, was already provided as an information document (INF document) for the recent online deliberations of the Subsidiary Body of	however it is not the place for this document to champion any particular distinction between them (see Section B. Scope and Methods).

			Scientific, Technical and Technological Advice (SBSTTA-24). We disapprove of using a document that has not been finalized as an information resource for official SBSTTA-24 deliberations.	
Public Research and Regulation Initiative (PRRI)	0	0	Without a common understanding of terms, analyses and discussions become meaningless. The not-endorsed operational definition on synthetic biology is broad enough to accommodate new advances in the emerging discipline but it offers no clear distinction from other biotechnologies. CRISPRs, like other genome editing tools, are not exclusive for synthetic Biology. They are used in diverse ways including in traditional modern biotechnology and in Precision Breeding/New Breeding Techniques. The text mixes genome editing, modern biotechnology, genetic engineering and gene drives as if they were all examples of synthetic biology. All the examples given in the document need a fact check whether they are indeed examples of Synthetic Biology. As with the definition of modern biotechnology within the CPB, it is probably useful to exclude related concepts as not synthetic biology. The possibilities from synthetic biology mindset range widely making broad generalizations impossible. More generally, the covid crisis has also shown the need to rethink rule-making to be more agile to harness the opportunities of innovation responsiveness in rapidly changing environments. We need careful consideration to decide if, how much and at which stage additional regulations are useful. One of the important provisions of the CBD is Article 16, which acknowledges the importance of access to relevant technologies can make a substantial difference in addressing biodiversity loss. Considering that developing countries are lagging behind to develop synthetic biology. It would be of interest to explore existing initiatives and in which ways to provide and/or facilitate access for and transfer of technologies that apply to the conservation and sustainable use of biological diversity to developing countries. Several citations are missing throughout the 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). Revisions made See section 8.1.6 on article 16 and 19.

Outreach Network for Gene Drive Research	0	0	**General Comment:** Gene drives are consistently characterised as being in the advanced stages of research or on the cusp of commercialization throughout the text. It is unclear what exactly is meant by "advanced stages", but gene drives are many years away from being deployed or placed on the market. The text should be revised to reflect the fact that no field trials of gene drives have yet taken place and any such test is likely years away, and that the most advanced gene drive applications currently under development are being developed by not-for-profit research consortiums, and will not be marketed on a commercial basis.	Comment noted. Revision made.
German Central Committee for Biological Safety (ZKBS)	0	0	1. The Technical Series No. 82 tries to identify developments in synthetic biology as well as potential gaps in the regulation of synthetic biology. However, it is very difficult to identify gaps without a widely accepted and clear definition of synthetic biology. The operational definition used by the CBD for deliberations has not been acknowledged by the COP as there was disagreement as to whether the definition can describe synthetic biology adequately. This definition was often described as too broad and covers all major areas of biotechnology including also traditional research and development projects which lack the novel aims and constructive endeavours characteristic of synthetic biology. These conventional and other biotechnology issues are long known, often use classic gene technology and are, if applicable, under the scope of the Cartagena Protocol. The German Central Committee for Biological Safety (ZKBS) substantially shares the concerns of a too broad definition of synthetic biology. In this regard, LMOs mentioned here include, for example, genetically engineered bacteria for agriculture, genetically engineered sorghum and oilseed rape, or genetically engineered bacteria for environmental applications. Further, genome-edited organisms cannot be considered synthetic biology, but are either exempted from GMO regulations (as decided by some Parties) or are LMOs (as decided, for example, by the EU). Furthermore, transient modification techniques such as "RNAi sprays" do not modify an organism´s genome and should not be considered synthetic biology either. The CBD may concentrate its efforts and resources on the identification of	Comment noted. The issue of there being no consensus regarding the definition of synthetic biology is recognised in the Scope & Methods, and the authors acknowledge that variations in interpretation by the Parties exists as well as how they are being applied.

			organisms, components and products that are not conventional LMOs and therefore cannot be dealt with under the scope of the Cartagena Protocol. 2. The ZKBS likes to emphasize that organisms containing engineered gene drive applications to circumvent agricultural pests or human diseases, e.g. malaria, and organisms resulting from genome editing must be kept apart and are both not per se an item of synthetic biology.	
DER VBIO & GASB	0	0	General comment VBIO, the German Life Sciences Association (www.vbio.de), represents the interests of professional societies in the life sciences, including teacher associations, with over 25,000 members of all life sciences backgrounds. GASB, the German Association for Synthetic Biology (https://www.synthetischebiologie.org), represents over 100 scientists and university students in the field of synthetic Biology. We advocate not only for the freedom of life science research, but also for its ethical, safe and secure conduct, as well as compliance of all stakeholders to all respective regulations. 1. Definition of Synthetic Biology VBIO and GASB have already commented on the topic of Synthetic Biology in the run-up to SBSTTA in 2018 (https://bch.cbd.int/database/record.shtml?documentid=113239). Regretfully we have noticed that, in the last three years, no observable progress towards a clear definition of Synthetic Biology was made. A clear distinction between methods and applications is missing throughout the text and both are subsumed under the generic term Synthetic Biology. In this regard, we consider the IUCN Assessment of Synthetic Biology and Biodiversity Conservation (https://www.iucn.org/theme/science-and-economics/our-work/other-work/synthetic-biology-and-biodiversity-conservation/development-iucn-policy-synthetic-biology/iucn-assessment-synthetic-biology-and-biodiversity) a more concise starting point for defining Synthetic Biology. Without a clear definition, a rigorous assessment of the claims and statements within this document is impossible. We are very much aware of the difficulties in finding a common definition. We take note that varying	Comment noted. See scope and methods for clarity on scope and the definition.

			definitions and terminologies are used in different countries. At the same time, we are also aware that the insistence on a generally agreed definition, as well as the argument that synthetic biology is not definable at all, are in themselves strategies to block the political process from moving forward. A possible way ahead and a lesson learned can come from the topic of Digital Sequence Information (DSI). At the last AHTEG on DSI (https://www.cbd.int/doc/c/ba60/7272/3260b5e396821d42bc21035a/dsi-ahteg-2020-01-07-en.pdf), four potential definitions for DSI were taken up as a starting point for discussions. Having several potential definitions, ranging from the narrowest to the broadest, would help to avoid inadmissible equivalencies being drawn (e.g., genome editing with gene drives), without the need to decide on a final definition. It could then be assessed for every definition whether Synthetic Biology is a New Emerging Issue and whether and what type of further regulation is needed. 2. Gene drives Gene drives can be a new tool to support conservation efforts, but at the same time they pose the highest risks for biodiversity. Defining what constitutes a Gene drive and what does not is difficult, but Alphey et al. provide a very good starting point (https://doi.org/10.1073/pnas.2020417117) that should be elaborated upon. In any case, gene drives are only one very specific tool of Synthetic Biology, even in the narrowest definition. A clear distinction should be drawn here, especially towards methods of industrial biotechnology that take place in contained settings. It may even make sense to separate the topics of Synthetic Biology and Gene drives, due to the large differences.	
Engineering Biology Research Consortium (EBRC)	0	0	It is important that the benefits and risks associated with synthetic biology are accurately communicated to regulators and the public. Synthetic biology has a long track record of being practiced safely and can potentially offer significant options to address challenges in heath, agriculture, environmental conservation, and climate and sustainability. These benefits and opportunities (https://doi.org/10.1016/j.tree.2016.10.016, https://roadmap.ebrc.org/2019-roadmap/) should be highlighted in the report. The report should also follow an evidence-based approach in assessing the	Comment noted. Revisions made.

			risks of genome editing and avoid generating overstated concerns about novel biological weapons (e.g. remove speculation about weapons genetically engineered to target certain populations, and make it clear that synthetic biology does not make it any easier to package, dry-down, mill, disseminate or persist a biological weapon.) Accurate, specific information is essential for developing broadly supported up-to-date risk management practices, science- and evidence-based risk assessments and proportionate governance, to be tuned to the different categories and applications mentioned in sections 2 and 3.	
EBRC	0	0	We recommend comprehensive updates in the following areas within the document to improve its readability, consistency, and identification of emerging gaps: ● Science and technology developments ● Application developments ● Regulatory developments ● Emerging themes and recommendations There have been significant scientific, technological, and applications developments in synthetic biology since the 2015 report of the Convention on Biological Diversity. We recommend the inclusion of these examples to provide an accurate representation of the current state of the field. [1] https://roadmap.ebrc.org/2019-roadmap/ [2] https://doi.org/10.1038/s41467-020-19092-2 We suggest the update to also include information on biosecurity incidents in the reporting and preceding period to enable evidence-based assessment of biosecurity risks and to provide information on regulatory practices and their effectiveness.	Comment noted. Revisions made.
EBRC	0	0	As the regulatory landscape around synthetic biology clarifies, it is important to stress that regulations help foster and guide the safe development of synthetic biology, but also do not unnecessarily deter innovation and beneficial applications. We would like to especially highlight the following three recommendation: ● Innovation often outpaces regulation. Regulatory systems must be able to	Revision made. The key messages section has been restructured.

			rapidly and appropriately respond to new technologies to enable deployment. CBD should enable critical, constructive debate leading to reasonable and implementable practices at short notice. ● While it is important to consider the economic, social, and cultural impacts associated with synthetic biology, CBD should consider these concerns together with the potential risk of stalling, delaying science and technology development, which are urgently needed to address global environmental, sustainability, and health challenges. ● The presentation of digital information in the report is a concern, due to a lack of transparency (definition of derivatives, origin/uniqueness of digital sequence information in databases) that may lead to confusion, require significant resources both from researchers and regulators and could hamper innovation and development of technologies to address global challenges. The discussion of digital information should be placed in context of the CBD's other studies: https://www.cbd.int/dsi-gr/2019-2020/studies/	
EBRC	0	0	We believe the governance and regulation of synthetic biology at the international level would benefit from a multilateral approach and recognize that no one entity is going to be able to handle the global regulation of Synthetic Biology methods, products, and deployments. To this end, we advocate for directly involved stakeholders coming to agreements where possible.We recommend the following: ● CBD should leverage participation from other international organizations which also address aspects of synthetic biology (e.g. WHO, CITES, IUCN). It is valuable that different views and approaches are developed with respect to risks and risk management so that over time best-practices can develop. ● Synthetic biology consortia (e.g. IGSC, EBRC) could play a key role, as they encourage standard behaviours amongst large numbers of relevant parties, spanning government, academia, and industry. These parties help steer the consortia and show encouraging adoption of norms. These do not replace government and international regulations and oversight, but they can provide solid groundwork from which regulations and oversight can be developed.	Revisions made. Key messages section has been restructured.

Global Industry Coalition	0	0	**General comments on the draft document** The GIC notes the review carried out by the authors that captures recent as well and earlier biotechnological applications and developments. We recognise that due to the lack of agreed upon definition of synthetic biology, and the very broad nature of the existing operational definition developed by the Ad Hoc Technical Expert Group on Synthetic Biology (AHTEG) in 2015, it is impossible to clearly draw a line between "synthetic biology" applications, and biotechnological applications more generally. The authors point out that they "recognise that some of the processes or products described in this document may not be considered as synthetic biology approaches and applications by all readers, however the broadest interpretation has been made in order to be as inclusive as possible whilst at the same time not championing this interpretation as being definitive. The authors have also attempted to achieve the same degree of inclusivity when presenting the numerous published perspectives concerning individual synthetic biology applications and the sector as a whole."[p.15, lines 20 -25]. The GIC believes that due to the approach taken, the draft is not an account of synthetic biology applications, but rather a presentation of any and all biotechnological developments in recent decades. Some of these "developments" are not recent and occurred well before the first Technical Series document of 2015 but were not included in that document. We therefore question the appropriateness of the title of the document as "synthetic biology". We do not agree with several of the applications that are included as synthetic biology in this updated document, but in particular emphasise our view that genome editing is not synthetic biology – it is a collection of enabling tools that may be used to achieve a range of outcomes. This document includes genome editing as a whole, including a commercial example containing a point mutation. Such genetic modifications are comparable to spontaneous mutations, or that which can be achieved using conventional methods, and cannot be considered within the scope of a "new dimension" per the operational definition, even at its broadest interpretation. We strongly recommend that the authors remove examples of applications of genome editing that result in plant and other products that are comparable to products	Comments noted. 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).

			developed with the application of conventional breeding tools, and have been determined by different regulatory authorities as not meeting the definition for a LMO. Our specific editing suggestions and recommendations presented below are intended to draw the attention of the authors to text that needs clarification with our objective being to reduce exaggerated, speculative or hypothetical statements, correct misleading references, and improve focus on actual developments since the publication of the first Technical Series No 82 in 2015. We note that this document was included as an INF document (CBD/SBSTTA/24/INF/19) in the recently convened formal virtual sessions of SBSTTA-24, despite it being a draft and not having completed peer review. The notification for peer review itself states: "Kindly note that the document is a draft, for comments only, and not for citation or other uses." We therefore question the appropriateness of including it in the SBSTTA INF materials.	
Biosafety South Africa	0	0	(1) The current document is critically flawed as it includes a wide array of technologies, applications and products that are NOT synthetic biology. Therefore, although the technical content related to these individual topics may be acceptable in isolation, their discussion in this context is inaccurate, confusing, and counterproductive in attaining the goals of the CBD. Auxiliary notes 1: a. The practice of and the term "synthetic biology", including its intended meaning, scope and distinction evolved from the availability of relevant technologies, the aims and the multidisciplinary tactics of its practitioners and it therefore has an established, distinct bio-technical basis, meaning and scope. Any attempt to arbitrary redefine it based on non-technical considerations, that may include regulatory scope or political compromise, will therefore inevitably be met with consistent, principled disapproval. Meaning that such an approach is highly unlikely to ever lead to an acceptable compromise, as is evident from the inability of these discussions to develop an acceptable definition for the topic under discussion. Any discussions on HOW something should be managed is secondary and subject	Comments noted. 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

			to WHAT is being managed. In addition, "synthetic biology" is a hazard (potential source of the risk) in this context. Using it as a broad composite term erodes its usefulness in terms of establishing sensible risk categories and implementing an effective risk analysis framework. b. These protracted discussions on "synthetic biology" w/o clearly defining synthetic biology and the excessive focus on process, has caused much uncertainty and confusion, particularly amongst those with limited experience in LMO governance. Including - (i) the creation of artificial and unnecessary complications and duplications in terms of the scope and mandates of the CBD & CPB, (ii) the logical categorisation of relevant biohazards, (iii) the principles and broad applicability of established risk analysis frameworks, etc. (2) Established CBD & CPB frameworks can be used more effectively to accommodate synthetic biology and the other technologies and applications discussed in the current document, while ensuring a science-based approach, the coherent implementation of risk analysis, administrative and, good governance principles, and most importantly, the best possible chance to establish appropriate governance systems under the CBD. Auxiliary notes 2: a. The CPB was established to safeguard the environment against the use of LMOs resulting from modern biotechnology. Given this broad definition, any living organisms resulting from the application of synthetic biology (given a clear bio-technical definition), are highly likely to be LMOs and therefore already subject to the CPB. To be clear, the potential products of synthetic biology should be considered a subset of LMOs and not vice versa. With such an approach the only outstanding issues would be - (i) in terms of scope, the identification of possible non-LMO products that may need to be addressed further and (ii) in terms of established risk analysis frameworks, the evaluation of organisms and systems for which no close comparators exist. b. Products of other techniques, e.g. some classes of genome editing, and divergent application, e.g. gene drives, with distinct risk profiles should then be defined on an individual basis to ensure governance requirements are concomitant to the potential risk comparative to more conventional induced genetic variation technologies, including selective breeding.	them. (see Section B. Scope and Methods).

Max Planck Institute for Terrestrial Microbiology	0	0	Please note that this document contains collected comments of members of the Max Planck Society and is accompanied by an additional document, in which we comment on several issues with the overall text: 1. Lack of clear definition of the term "synthetic biology" and motivation to differentiate from existing regulatory processes 2. Need of a clear statement on the regulation of synthetic biological applications (Products or methodology should be evaluated?) 3. Lack of commitment to objective, fact-based decision-making for regulatory affairs 4. Weighing risks and benefits fairly, including discussion of alternatives during decision-making 5. Problems of limitations of scientific freedom and open science through overarching regulations 6. Problem of economic considerations impeding basic science 7. Intransparent review process and lack of participation of experts	General comment noted. Revision made.
BASF	0	0	I would like to thank the Secretariat for the opportunity to make inputs on the Synthetic Biology draft document. Considering this draft is intended as an update of the Technical Series on Synthetic Biology No. 82, it would have been better to circulate the draft highlighting the changes that have been incorporated for ease of reference. Given the tight deadline, comparing the original to the new has proved to be tedious and time consuming. An example of a challenge experienced is the review of the current state of synthetic biology. Some of the applications sited were released before the first publication, it is thus not clear whether that portion of the text was adopted from the previous document or it is indeed part of the new thinking and inputs. Also, by their own admission, the authors have broadened the definition to be all encompassing resulting in a review of all biotechnological applications beyond the scope and intentions of this task. As such, this document cannot be considered an update of the 2015 document.	Comment noted. 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

			It is recommended that the authors, at the very least, limit their task to the operational definition of synthetic biology developed by the AHTEG (even though not globally accepted) which, would have exclude genome editing as an application of synthetic biology.	them (see Section B. Scope and Methods).
Third World Network	0	General comment	In general, benefits are over-emphasised throughout the report, going beyond existing evidence. Superfluous use of descriptors such as 'precise' and possessing 'genuine potential' should be avoided.	Comment noted. Revisions made.
Third World Network	0	General comment	There are also projects aiming to develop self-spreading vaccines that have not been included in the report but are directly relevant to this topic and we suggest that they are incorporated. See for example: https://thebulletin.org/2020/09/scientists-are-working-on-vaccines-that-spread-like-a-disease-what-could-possibly-go-wrong/	Comment noted.
Third World Network	0	General comment	Reference to Ching, L. L., & Lin, L. L. (2019). Gene Drives: Legal and Regulatory Issues. Third World Network. https://www.twn.my/title2/books/Gene-drives.htm should be changed to: Lim, L.C. & Lim, L.L, and in the text referred to as Lim & Lim (2019) rather than Ching & Lin (2019).	Revision made
African Centre for Biodiversity	0	General comment	The report must be evidence based and must not go beyond the current evidence. Currently the document provides speculative and unfounded emphasis on the benefits of the technologies, which is not backed by current evidence. We urge that any potential yet-to-be established benefits are not conflated with demonstrable efficacy. Further to this, the report under emphasises the risks. This must be avoided to avoid bias. All phrases which imply benefits while underplaying the levels of uncertainty surrounding these technologies must be rephrased to indicate levels of uncertainty. This is further problematised by the fact that there are many viable alternative solutions to the problems that synthetic biology is aiming to address, making	Comment noted. Revision made.

			it seem as if synthetic biology is the only option, which is again misleading and incorrect, and disregards alternative pathways and future scenarios.	
African Centre for Biodiversity	0	General comment	There is a general assumption that future scenarios will include the application of synthetic biology, despite the fact that the need for synthetic biology is still to be demonstrated. This is unfounded, and should be rephrased to avoid being misleading.	Comment noted.
African Centre for Biodiversity	0	General comment	The report fails to explore the multi-disciplinary expertise required to address the risks inherent with synthetic biology. While there is recognition for the need to have an assessment based on economic, political, moral and ethical concerns, this is to be done on a case-by-case basis. This fails to ensure an assessment framework which is able to incorporate these aspects, and will result in fragmented and limited evaluation. We believe the case-by-case risk assessment is incredibly limiting to fully understand the widespread impacts from this technology. There are global risks that must be highlighted and serve as guidelines for all risk assessment, which include economic, political, moral and ethical concerns.	Comment noted.
African Centre for Biodiversity	0	General Comment	While the issue of Free, Prior and Informed Consent (FPIC) is referred to and acknowledged, the report fails to grasp the controversies and failings around FPIC in current engagement processes. Currently, there are many cases leading to conflict of interests and indeed local conflicts as a result of poorly conducted processes to ensure FPIC. The issue of conflict of interest must be addressed in the report, particularly when FPIC processes are done by the developers of the technologies. FPIC must be done by parties without economic interest, and by the promoters of the technology, and must ensure the participation of a wide range of rights holders including indigenous peoples and local communities, including farming communities. It is also vital that the right to say no is respected, without intimidation, or other coercive methods being used.	Comment noted. The importance of and challenges associated with FPIC is covered in the report, particularly section 5.1.2.
African Centre for Biodiversity	0	General Comment	The use of "science-based" in the context of risk assessment of LMOs is limited to just one specific methodology, and should be clearly defined. This	Comments noted.

			is often misleading as overarching "science-based", which could encompass a range of empirical methodologies. Limiting assessment to one narrow methodological approach, is not only incredibly biased, but is not inherently scientific. It is important that the scientific methods used for assessments are not restricted to one method, and the dominant method used by the developers of the technologies, but incorporate a range of interdisciplinary methodologies, reflecting the totality of scientific knowledge that should be used when assessing synthetic biology products for general release/commercialisation.	
Federation of German Scientists & ENSSER	0	General comment	The report lacks balance, it shows a strong bias towards assumed benefits without acknowledging its own assumptions and without providing the required scientific basis and analysis. Throughout it exaggerates benefits and possibilities of synthetic biology and its applications. There is often little actual information to back up assertions and when making them, the report would benefit from clarifying whose opinions these are and keeping its own distance, ie not presenting these interpretations as its own, but offering different sides and interpretations in an honest manner. It unfortunately comes across as suffering from an inability to distinguish between exaggerated claims and actual possibilities.	Comment noted. Revisions made.
Federation of German Scientists & ENSSER	0	General comment	Fails to provide the full picture, range and intricacy of the issues, concerns and risks It lacks contextualisation in terms of differentiating between symptoms (as a result of underlying problems) and the problems themselves and their underlying causes - and the search for sustainable, long-term solutions, which will require change of practices and the ecosystem approach. It seems to favour technical 'solutions' over the (eco)systems approach and fails to give space to or even acknowledge other paths and practices towards real solutions, e.g. in agriculture and climate adaptation. Here traditional knowledge, especially that of Indigenous Peoples and local communities and smallholder farmers has a critical role to play. The term "application(s)" would benefit from a clear definition either	Comments noted.

			throughout or whenever it is used, as its use and meaning is not uniform throughout the report. It may mean each time a technology is used, it may mean a general area of use, etc ... Please check and adjust.	
Action Group on Erosion, Technology and Concentration (ETC Group)	0	General Comment 1	Goes beyond the available evidence of the alleged benefits of Synthetic Biology (also called Synbio) while under-emphazising the risks to an extent that is misleading when read overall. Passages are phrased in a way that implies benefits are likely, underplaying the high level of uncertainty that surround many applications of Synbio. Assumes future environments will inevitably include Synbio applications, even though the need for Synbio has still not been demonstrated.	Comment noted. Revisions made.
ETC Group	0	General Comment 2	Fails to mention viable alternative solutions to the problems that are supposed to be addressed with Synthetic Biology applications, thus giving the impression that Synbio is the only option. It disregards other pathways, such as those based on the affirmation of food sovereignty through community, small holders and Indigenous Knowledge systems.	Comment noted. Revisions made. see Scope and Methods.
ETC Group	0	General Comment 3	Only makes one mention of the fact that issues of risk inherent in Synbio technologies cannot be dealt with by science alone. Does not explore the social and ecological aspects of the risks that are inherent in Synbio. These include: promoting artificiality and more uniformity in food crops and systems, more monoculture plantations which negatively impact biodiversity, the use of bio-vats instead of natural production, higher energy usage, higher dependency on proprietary seeds, organisms and applications.	Comment noted. Revision made.
ETC Group	0	General Comment 4	Recognises the need for assessment based on economic, political, moral and ethical concerns, but says this will have to be case-by-case, rather than looking at the area as a whole in order to establish a global assessment framework and not allow a fragmented and incoherent evaluation to happen in each case and each place. This is non-sensical as it assumes that there will not be risks that are generic, as there are in conventional GMOs and LMOs, for example.	Comment noted.

ETC Group	0	General Comment 5	Refers to Free Prior and Informed Consent (FPIC), but fails to acknowledge the fundamental difference between current engagement processes, undertaken by those developing the technology (leading to a conflict of interest), and the principles of FPIC which underlie genuinely participatory processes of technology assessment. This conflict of interest must be acknowledged in the report. An honest FPIC process would not be commissioned by the technology's promoters and others who stand to profit of the technologies, but instead by a wide range of rights-holders, including Indigenous peoples and local communities.	Comment noted.
Global Industry Coalition	01	06	Replace "*cell*" and "*genome*" with "*cells*" and "*genomes*".	Editorial suggestion noted and revision made.
Global Industry Coalition	01	22	Replace "*request that the present edition attempts to address*" with "*the present edition attempts to address this request*".	Editorial suggestion noted and revision made.
WHO	02	Section 6.2.2.	Perhaps "use of lethality" should read "use of virulence factors"	Editorial suggestion noted and revision made.
WHO	02	Section 7.1	Perhaps also insert "self-monitoring"	Comment noted.
WHO	05	41	"call" should read "calls"	Editorial suggestion noted and revision made.
UN Div. Ocean Affs.	06	01	Change "Biodiversity beyond national jurisdiction" to "Biodiversity of areas beyond national jurisdiction"	Revision made
Global Industry Coalition	06-07	-	**ABBREVIATIONS AND ACRONYMS** Move IGC up OPCW – missing text Delete 1 after ZFN	Editorial suggestion noted and revision made.
UK EBLC	08		The summary sets out the settings for application as being (i) contained, (ii) managed and semi-managed and (iii) unmanaged or wild. This ignores the medical setting, which given the context is fundamentally different from the description of the managed and semi-managed settings. There are important areas of development in microbiome and cancer therapies that are completely	Comment noted. See scope and methods for more details on the scope of the document.

			ignored in this report. This should either be stated that this is deliberately excluded, and reasons given, or be included and discussed appropriately.	
Global Industry Coalition	08-15	0	**EXECUTIVE SUMMARY – general comments** The executive summary presents a biased account of the content of the report and requires editing to reflect factual information presented in the body of the document. It should better reflect that: • there is no agreement on the next steps forward. • synthetic biology is not a single entity/discipline and as such different groups define it in different ways. • the definition of synthetic biology used in support of the continuing work on the topic under the CBD is not endorsed by Parties and is thus "work in progress". • remove speculative statements about gaps in regulation and use of technologies, as well as their impact • edit text to correctly depict enabling tools and technologies A more balanced view should be presented in the summary and specific edits are suggested in the following rows. We also suggest that rather than merely stating that this document is an update [page 9 line 12], there should be a paragraph providing an overview of the new information this "updated" version of the document provides compared to the 2015 version. We also recommend that an explanation and justification is provided for why this document has focussed on genome editing applications, especially such that are not considered LMOs, or such that are clearly captured and handled within the scope of existing LMO provisions. The extensive focus on such applications reduces the value of the document that is expected to provide updated technical information of applications of synthetic biology.	Revision made.
UK EBLC	08	01-48	Synthetic biology in this section is framed only in risk terms, but it is important to note that it can directly help protect biodiversity. For example by reducing the need to use broad-spectrum chemicals for agriculture and by reducing the extent of damage to the natural environment in pursuit of rare chemicals by enabling their synthesis instead of extraction in minute quantities from plants grown in sensitive regions.	Revision made.

PRRI	08	02	There is no agreed-upon definition of Synthetic Biology. As a relatively new mindset, it is loosely defined as the discipline evolves. It is important to note upfront that this operational definition of Synthetic Biology was not endorsed by parties. It fails to clearly distinguish Synthetic Biology from other biotechnologies or even tools used among different disciplines. This makes the document confusing.	Comment noted.
PRRI	08	05	The "advance rapidly and expand beyond the confines of the laboratory" is an assumption that it is contradictory to the limited number of existing examples given later in the text. In addition, the examples given are a mixture of modern biotechnologies, precision breeding (New Breeding Techniques), Synthetic Biology. It would be correct to write that there is substantial interest in Synthetic Biology which can be indicated by the number of publications, ... But strong interest in the emerging discipline does not yet necessarily translates into "rapidly expand beyond the confines of the laboratory" as one can see further down in the text which identified only very few examples of products resulting from Synthetic Biology.	Revision made
Imperial College London	08	05	Synthetic biology is not one discipline, it rather includes a combination of disciplines (mol. biology, engineering, biophysics and many others)	Revision made.
India Water Foundation (IWF)	08	06	Source should be mentioned for the argument of synthetic biology being a potential risk.	Comment noted.
Max Planck Institute for Terrestrial Microbiology	08	06 ff	A potential risk to biodiversity only arises from the release of organisms to the unmanaged or wild setting. As such, any product (either created through classical breeding, GMO or synthetic biology) should be treated equally, especially since product created through single-base editing are in principle even better controlled. It should also be noted that CRISPR/Cas9 gene editing efforts that result in single-base changes, which are also naturally occurring and/or could be the result of spontaneous mutation are not considered GMO.	Comment noted. See section D regarding impacts. See also scope and methods.

Federation of German Scientists & -ENSSER	08	06-07	The phrasing "the potential of synthetic biology carries hopes and aspirations to address a multitude of global challenges related to ...." is merely an opinion about the potential of synbio that is not agreed by all, nor is it viewed as the instrument of choice to address the global challenges and multiple crises. The overemphasis on benefits and the effort to portray synthetic biology applications as solutions means the reader cannot easily see the broad picture and the context in which the debate and the crises are happening. The importance of a systems approach and the ecosystem approach to many of the challenges is not given any space. Yet we would require exactly that bigger picture and the analysis within the systems approach to understand and assess the examples presented in this report.	Comment noted
Expert committees of DFG	08	06-8 & 15-20	In principle a potential risk to biodiversity would only arise from an organism that is released to the environment (in the sense of an unmanaged or wild setting). The remainder is just carried out comparable to normal agriculture, animal production. As a general thing and given that by definition one knows the produce in principle perfectly or better (synbio) than when making (natural) hybrids, etc, the guidelines to be applied in all three contexts, should by no means be harsher than those applied to any other modified or unmodified organism.	Comment noted. See section D regarding impacts and Section E regarding regulatory approaches.
GJSG on SynBio	08	6-8 & 15-20	In principle a potential risk to biodiversity would only arise from an organism that is released to the environment (in the sense of an unmanaged or wild setting). The remainder is just carried out comparable to normal agriculture, animal production. As a general thing and given that by definition one knows the produce in principle perfectly or better (synbio) than when making (natural) hybrids, etc, the guidelines to be applied in all three contexts, should by no means be harsher than those applied to any other modified or unmodified organism.	Comment noted. See Section D regarding impacts and Section E regarding regulatory approaches.
Centre for Doctoral Training in BioDesign Engineering, UK (CDTBE-UK)	08	08	It could be argued that synthetic biology, rather than being a risk for biodiversity, could actually expand and/or maintain biodiversity by, for example, preventing the extinction of endangered species.	Comment noted. Potential benefits are discussed in section 4 along with the potential risks. De-extinction is addressed in 3.2.3 (e).

Western Michigan University	08	08	Regarding the term "potential risk" used here and throughout the document: the concept of potential (i.e. possible) is already incorporated in the definition of risk. Thus potential risk is simply risk. The terminology should be adjusted accordingly.	Revision made.
IWF	08	08	Studies shows that synthetic biology is rather helpful in preventing extension of endangered species.	Comment noted. Covered in sections 3.3.1 and 4.
Imperial College London	08	08	As it stands this statement sounds as if this is some unique risk associated with these modern technologies. It is not. Other conventional interventions such as pesticides can have a great impact on biodiversity. Also, there are synthetic biology approaches that are aimed at conservation and restoring biodiversity (e.g. against invasive species in Australia), therefore it is not precise to put them all under the generic umbrella of causing a potential risk to biodiversity.	Revision made.
Federation of German Scientists & ENSSER	08	08	"about ~~potential~~ risks...": delete "potential" as risks are defined as the likelihood of a harm to occur, i.e. it already entails the "potential"	Revision made.
Max Planck Institute for Terrestrial Microbiology	08	09 ff	A fundamental difficulty with the text is that it does not precisely define synthetic biology and make a clear case why it should be regulated differently from processes such as GMO, genome editing (CRISPR-cas9) and gene drive that are already widely discussed by regulators. This is already an issue in the Executive summary, where it is vaguely mentioned that synthetic biology (page 8 lines 9-20) "relies on a suite of supporting technologies and tools" but the only specific examples mentioned are CRISPR-cas9 and gene drive. Also, on pages 30-34 most of the examples given are straightforward use of CRISPR-cas9 for single gene knock outs. The authors seem aware of this (page 15, line 21), as the document states "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". But the breadth of the definition makes the document very difficult to assess or engage with. I suggest that they provide a clear, precise definition of synthetic biology as they interpret it and state exactly how this differs from the specific technologies they mention that are already heavily discussed by regulators.	Comment noted. The document uses the operation definition as per the scope and methods.

Global Industry Coalition	08	10	**Delete** "genetic engineering" at the end of first sentence and add text: "*….the relatively long-established field of genetic engineering - the foundation of synthetic biology*."	Revision made.
Federation of German Scientists & ENSSER	08	10	~~Sophisticated~~ perhaps say 'advanced' -	Revision made
Global Industry Coalition	08	10-12	**Delete** "*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*" and **replace with** *"The more recent emergence of increasingly sophisticated technologies and tools has greatly expanded the potential range of applications, and facilitated.... "* The text is exaggerated and focused on genome editing .	Revision made
ISF	08	10-15	Particular reference is made on "genome editing technology" and "CRISPR/Cas technology" as methods of synthetic biology. Focusing on particular methods is not justified since, as noted above, these methods can be applied to achieve a large variety of outcomes, many of which will be close to or even identical to what can happen through processes in nature or conventional plant breeding. Please revise to highlight that these are enabling technologies and only some of their applications (in conjunction with other methods) may be "synthetic biology"	Comment noted. Revision made.
PRRI	08	11	Genome editing is a group of technologies/tools to change an organism's DNA. They are by no means exclusive for the use on Synthetic Biology. These technologies allow genetic material to be added, removed, or altered at specific locations in the genome. If it is used to add a gene the resulting product can be a LMO. It can be also used for targeted mutagenesis in precision breeding or New Breeding Technologies.	Comment noted and revision made.
Federation of German Scientists & ENSSER	08	11	"applications" - please clarify what is meant and that this refers to research settings, not applications in the 'real world' so to speak.	In this document, an application is referred to the practical use

				and not to a formal request or dossier
Federation of German Scientists & ENSSER	08	12	"has increased exponentially" - who says so? It is also not referenced later. Are you referring to number of publications? And over which time period?	Revision made
ETC Group	08	13	The listed benefits in agriculture are speculative and dependent on which farming system is used (i.e. not the one used by the majority of small holders / peasants in the world). Yet these benefits are stated as fact.	Revision made.
African Centre for Biodiversity	08	13-14	The benefits listed are speculative yet stated as fact. This must be rephrased accordingly, and taking into account different farming systems they are being applied to. The statement that CRISPR-Cas technology is already having impacts on agriculture is unfounded and speculative and should be rephrased to explicitly state that impacts on agriculture are yet to be demonstrated and explored.	Comment noted and revisions made.
Expert committees of DFG	08	13-15	It is unclear why CRISPR/Cas9 gene editing is discussed in an agricultural context here. Most of what is currently done by gene editing does not involve the transfer of foreign DNA to the final product and hence in many countries is not considered under GMO legislation. Genome-editing approaches that do not introduce foreign DNA should not be considered in the context of synthetic biology. This is also clearly different from ensuing text on gene-drives, which clearly is an entirely different category of genetic engineering. Like in many other parts of the document, genome editing is confused with gene drives and GMOs.	Comment noted and revisions made
GJSG on SynBio	08	13-15	CRISPR/Cas9 and other genome-editing approaches that do not transfer foreign DNA into genomes hardly meet the criteria of a "synthetic" biology. In a number of countries, the resulting products do not fall under GMO legislation at all.	Comment noted
Global Industry Coalition	08	13-15	It is highlighted that "*Particularly, CRISPR-Cas technology is "having impacts"*…" We do not agree with singling out one type of enabling technology, which is not yet widely demonstrated or "having impacts" despite being an active	Comment noted and revision made

			R&D area. We also question the emphasis on potential agricultural applications. We suggest that the text should be made clearer that: i. this is an enabling technology and not all applications will be "synthetic biology". ii. what is presented here are potential beneficial applications of certain tools.	
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	08	13-15	„Particularly, CRISPR-Cas technology is having impact in agriculture, especially in increasing plant yield, quality, disease resistance and herbicide resistance, breeding, and accelerated domestication.“ Consider to replace “is having” for “is expected to have” as by now there is no CRISPR-Cas-based genome edited plant available on the market worldwide.	Comment noted and revision made
Federation of German Scientists & ENSSER	08	13-15	“ .. is having impacts in agriculture, especially in increasing plant yield, quality, disease resistance and herbicide resistance, breeding, and accelerated domestication.” CRISPR/Cas technology has not yet had any impact on agriculture. There are no CRISPR-modified crops in the fields. There is no data on real life performance trials (including under different environmental conditions, in the presence of different biotic and abiotic stressors, and across a longer time span) of genome edited modified crops that shows yield increases (what please is meant by “plant” increase?) that would allow for such a statement. This statement needs removing or urgent adjustment - as it does not depict the reality. Furthermore, ‘accelerated’ domestication comes with its own risks and it will require much further work and investigation to assure safety and reliable agronomic performance with such an approach.	Comment noted and revision made
Third World Network	08	14	The statement that CRISPR-Cas technology is already “having impacts on agriculture” is not correct, but is instead based on speculative future aims of the technology. There are currently only two fully commercialised genome edited crops (neither or which have been developed with CRISPR systems), one is CIBUS’s herbicide-tolerant canola and thus designed to promote the use of chemical pesticides, and the second, CIBUS’s “high-oleic acid” soybean variety with unproven health benefits (oleic acids already present in other common oils). Neither crop has been shown to have impacts on “plant	Revision made

			yield, quality, disease resistance", but only "herbicide-tolerance" which in itself represents a clear risk to biodiversity, by increasing the use of synthetic pesticides. Neither crop is widely cultivated and CIBUS soybean is suffering from a lack of adoption by farmers. It is of fundamental importance that unsubstantiated claims of genome editing are not used here to give an inaccurate representation of the state of R&D, particularly in the executive summary, which sets the tone of the rest of the document. This should be altered to acknowledge explicitly that impacts on agriculture are yet to be demonstrated. We suggest the sentence (lines 10-15) is altered to: "Crops are currently in development that aim to have positive impacts on agriculture. As a consequence, the number of applications in development, especially those that make use of genome editing technology, has increased exponentially and has led to research advances in plant and animal engineering, personalised medicine, and clinical therapeutics. Particularly, CRISPR-Cas technology is being explored for potential impacts on agriculture, especially in increasing plant yield, quality, disease resistance and herbicide resistance, breeding, and accelerated domestication, though the vast majority are in the discovery phase with demonstrable evidence of efficacy or commercialisation of products currently lacking."	
Imperial College London	08	15-16	"Can be applied" as "tool to spread through a population". This implies that these engineered gene drives are ready to be released, which is not the case. All experiments and results so far have been obtained from contained lab populations.	Revision made
CDTBE-UK	08	16	Could comment on which types of traits are being spread (e.g. inability to transmit Plasmodium, the malaria-causing pathogen in Anopheles).	Kindly refer to section 3.2.2 (b).
UK EBLC	08	16	Could comment on which types of traits are being spread (e.g. inability to transmit Plasmodium, the malaria-causing pathogen in Anopheles), noting including dengue-fever, yellow fever, chikungunya and Nile Fever as mosquito populations spread their habitats away from their native origins into formerly more temperate regions as a result of climate change.	Kindly refer to section 3.2.2 (b).

IWF	08	16	Examples can be provided for the traits and organisms.	Kindly refer to section 3.2.2 (b)
PRRI	08	16	Gene drives are not engineered in all types of organisms due to practical and technical reasons. For a gene drive to spread, sexual reproduction is a prerequisite, and a short generation time is highly favourable. While the range of synthetic gene drives have been shown to be functional in laboratory experiments in larger number of species. To write that "gene drives can now potentially be applied to a wide variety of organisms" is exaggerated.	Revision made
Global Industry Coalition	08	16	A "*wide variety of organisms*" is also not demonstrated. The text needs to be toned down and factual. The proofs of concept for engineered gene drives remain limited to a small number of insects.	Revision made
Global Industry Coalition	08	17	**Insert** "*potential*" prior to "*synthetic biology*".	Revision made.
Global Industry Coalition	08	19	**Delete** "*several*".	Revision made.
Western Michigan University	08	21	Throughout the document: substitute the word "discipline" with "category". "Discipline" implies an organized or recognizable area of endeavor, but since the definition of Synthetic Biology is still under discussion even under the CBD, with only a working definition agreed upon for the purpose of facilitating discussion, Synthetic Biology cannot be considered a discipline for the purposes of this document. Page 9, lines 21 and 22 also supports the lack of consensus on what Synthetic Biology is, and therefore the lack of what would constitute a discipline. On page 10, lines 14-20, a long list of technologies and tools that are described to be within the scope of synthetic biology is given. The items in the list are referred to as disciplines. Those lines contradict the statement here that refers to synthetic biology as a single discipline. Therefore, while the statement that synthetic biology is often referred to as a single discipline might be true, it is important to state that synthetic biology is not a single discipline.	Revision made.
PRRI	08	21	synthetic biology is often referred as a **multidisciplinary** (not a single discipline) approach or area of research. It is better understood as an umbrella term or a mindset.	Revision made.

Global Industry Coalition	08	21	**Delete** beginning of the sentence "*although synthetic biology is often referred to as a single discipline*" as it is not considered to be a single discipline but rather it is generally recognized as a combination, as stated above in line 3.	Revision made.
Global Industry Coalition	08	22	**Replace** "*represent a wide array of potential impacts*" with *"... have the potential to result in organisms and products with a range of potential impacts of relevance to the CBD.*"	Revision made.
Global Industry Coalition	08	22	**Replace** "*are*" with "*may be*".	Editorial suggestion noted.
PRRI	08	22-24	The part "some of which are complex in nature … potential impacts." Can be deleted because is vague, and in the phrases that follow presented in more detail.	Revision made
Federation of German Scientists & ENSSER	08	23	This is not just to "support the discussions" but to support the assessment and the ongoing deliberations	Revision made.
ETC Group	08	25	Ignores known risks that are built into the very design of many Synbio applications (e.g. risk of grave loss of biodiversity through engineered gene drives). Instead of calling for the assessment of these risks to take place in the phase where technologies are still being conceptualised and/or developed, the paper states that only case-by-case risk assessment might be enough, implying this could happen after they have already been developed.	General comment noted
Global Industry Coalition	08	25	**Insert** "*there are views that*" after "*Therefore,*".	Editorial change done
African Centre for Biodiversity	08	25	This ignores the documented risks inherent in many synthetic biology applications, such as risks of spreading through populations and between species in the case of gene drives, with massive risk to biodiversity.	Comment noted. Text about potential risks is further developed in Section 4 and in Section 5 on socioeconomic considerations.
Global Industry Coalition	08	26	**Replace** "*is seen as*" with "*should be*". **Delete** "*one*".	Revision made

Federation of German Scientists & ENSSER	08	26	'science based assessment' - this concept requires a broad interpretation, not a narrow one, in order to ensure the inclusion of different knowledge systems and a broad multi- and inter-disciplinary process.	Comment noted.
ETC Group	08	26 and elsewhere	The use of "science-based" in the context of assessment should be more thoroughly defined to acknowledge that what is referred to is just one specific methodology. Limiting assessment to one narrow ideological view point is not scientific in the normal sense of the word, but scientism. It is vital that the methodology of 'science' that will be used for assessments is not restricted to the dominant method being used by developers of synbio products, but is instead interdisciplinary, reflecting the totality of scientific knowledge across nations and territories that may be targeted for releases/commercialisation of future Synbio products. This comments is in alignment with others from other NGOs.	Comment noted.
Third World Network	08	26 and elsewhere	There reductive use of "science" based assessment should be more thoroughly defined to either acknowledge that this indeed refers solely to one specific scientific epistemology. A universal framing of "science", is not only highly biased, but also limits the quality of assessment to one narrow ideological view point. It is vital that the type of 'science' that will be used for assessments is not restricted to the dominant form being used by developers of synbio products, but instead reflects the totality of scientific knowledge across nations and territories that may be targeted for releases/commercialisation of future synbio products.	Comment noted.
Global Industry Coalition	08	27	**Replace** "*evaluates such*" with "*incorporates broader considerations such as..*".	Revision made.
Global Industry Coalition	08	27-28	**Delete** "*alongside a scientific analysis of the expected or potential changes that would result from using technology*.".	Comment noted.
Global Industry Coalition	08	28	**Delete** "*also*".	Revision made.
Global Industry Coalition	08	28-29	**Delete** "*due to the diverse nature of the*".	Comment noted.

Federation of German Scientists & ENSSER	08	28-30	Please adjust to clarify and present that there are categories and groupings with common factors that would benefit from an overall assessment, in order to understand which questions need to be asked, how to identify potential harms and which potential harms should be considered and how to assess them. This is also behind the need to provide guidance materials for risk assessment and risk management for specific categories of LMOs. It should only be after such wider assessments and considerations, and in that context, that individual applications can move forward on a case-by-case basis.	Comment noted.
Global Industry Coalition	08	29	**Delete** "*they*".	Comment noted.
Global Industry Coalition	08	31	**Delete** *"commercial deployment and".* It should be noted that many applications will be deployed in a not-for-profit way.	Revision made
PRRI	08	31-35	When and if regulations for innovation and emerging technologies are needed should be considered carefully to simultaneously unlock the potential benefits while protecting public interest. The statement on lines (31-35) gives the misleading impression that Synthetic Biology reaching commercial development and environmental release alone present an immediate need to be regulated in some other way. The current or near market living organisms resulting synthetic biology fall into the definition of LMOs under the Cartagena Protocol and are therefore regulated. Other products like pharmaceuticals, chemicals, etc. are likely to be covered by other instruments. If there are concrete exceptions that were singled out, it should be clearly stated.	Comment noted
Global Industry Coalition	08	32	**Replace** "*same*" with "*existing biotech regulatory*".	Revision made
Federation of German Scientists & ENSSER	08	32	"classical genetic engineering" - this term is misleading and rarely used. It could be "first generation" or simply "previous" - although it is still a current form of genetic engineering.	Revision made
Global Industry Coalition	08	32-33	**Delete** "*classical genetic engineering albeit*". The authors use the term "classical genetic engineering" which is not defined and has the potential to be understood differently by different readers. We	Revision made

			recommend that the authors do not use this term anywhere in the text of the report, especially when they refer to applications of modern biotechnology that result in LMOs. This term can also misleadingly imply that the existing regulatory and governance mechanisms apply only to such “classical" applications, however these remain applicable for all applications of genetic engineering.	
Expert committees of DFG	08	32-34	Again, here it is ignored that by definition of a synbio product, one knows much better what has been modified. It´s part of the modelling process in the design phase and in the evaluation of the product. This is how some regulatory bodies evaluate synbio feedstock/food.	Comment noted.
GJSG on SynBio	08	32-34	Synthetic biology products are rationally designed products whose genetic modifications are precisely known which is the basis of evaluations by some regulatory bodies.	Comment noted.
Global Industry Coalition	08	33	**Insert** "*or without*" after “*with*”	Revision made
Global Industry Coalition	08	33	**Delete** “*a*” before “*national*”	Revision made
Federation of German Scientists & ENSSER	08	33	Please replace ‘albeit’ with “, possibly” - as it will depend on future deliberations and the decisions made by individual parties.	Revision made
UK EBLC	08	35	This statement conveys the implication that synthetic biology is an entity that needs specific governance, and that the differing rates of framework development somehow imply a lack of governance, when in fact the differences are often not a result of a lack of technical data but relate to regional interpretations (cf regulations on gene editing). It should be noted that for the vast majority of products, synthetic biology merely serves as an alternative channel for design and production, and that relevant regulations such as food safety standards, apply. We feel that an over complicated/stringent regulatory framework might cause irreparable damage to the discipline and substantially delay translational efforts. We have argued in [1,2,3] of ways in which the process of research (and hence translation) could be made more responsible, transparent and	Comment noted. Revision made.

			robust without stifling regulation. [1] *Linking Engineered Cells to Their Digital Twins: A Version Control System for Strain Engineering.* **ACS Synth. Biol.** 2020, 9, 3, 536–545, 2020, https://doi.org/10.1021/acssynbio.9b00400 [2] *For the sake of the Bioeconomy: define what a Synthetic Biology Chassis is!* **New Biotechnology**, 2020, 60,https://doi.org/10.1016/j.nbt.2020.08.004. [3] *Versioning Biological Cells for Trustworthy Cell Engineering*. **bioRxiv** 2021.04.23.441106; doi: https://doi.org/10.1101/2021.04.23.441106	
Global Industry Coalition	08	40	**Replace** "*fragmented*" with "*complex*". The review made by the authors does not lead to a conclusion that there is a "fragmented landscape" and the statement is more speculative than factual.	Editorial suggestion noted.
Global Industry Coalition	08	41	**Replace** "*creates a complex scenario with the potential for regulatory gaps and* areas of convergence to develop." with "*…has aroused the concerns of some that there could be gaps in regulatory oversight. Yet, it is also recognized that there may be areas of convergence that call for greater coordination and collaboration between international organisations on issues of overlapping concern.*" This is edited to reflect that "gaps" are not a widely held concern. This is evident in more than a decade of CBD work programs on synthetic biology involving extensive discussions on this exact topic.	Editorial suggestions noted and revision made.
Western Michigan University	08	47	"...appear ill-equipped…" is not a conclusion that can be made, nor within the scope of this document.	Revision made.
IWF	08	47	The statement need more source and conclusive evidence.	comment noted.
Max Planck Institute for Terrestrial Microbiology	08	42 ff	It is unclear, why synthetic biology is singled out compared to other human activities affecting biodiversity (e.g. agriculture, plant breeding, land use, etc.), especially given the fact that synthetic biology or more accurately (single-base) genome editing is much more precise and targeted than traditional plant breeding efforts. The product and not the method that was used to create the product should be evaluated.	Comment noted.

Expert committees of DFG	08-09	42-2	It is deeply problematic and questionable to associate CBD with regulatory oversight on synthetic biology. Does not make sense at all to us. In which respect is it any different with respect to biodiversity than any generic human (agricultural) activity carried out over the past 10,000 years? In our opinion, synthetic biology is much more targeted and controllable than traditional breeding or biotech approaches.	Revisions made.
GJSG on SynBio	08-09	42-2	Synthetic biology tools allow for the rational, targeted design of production organisms, including plant cells and plants, far exceeding the precision of traditional breeding and genetic engineering methods. Given the various options of controlling the emergence of unwanted traits, regulatory oversight of synthetic biology in agriculture shall at least not be more restrictive than it is for conventional breeding.	Comment noted
Max Planck Institute for Terrestrial Microbiology	08	44 ff	"*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.*" This comment seems poorly defined and delimited. Moreover, these broader issues certainly require an analysis of each potential product individually and not the process of synthetic biology. Vagueness on these societal issues also arises later on page 11 (line 15), where no detailed examples or references are used to raise a number of hypothetical potential problems. "There may be the need to consider creating rules for specimens produced from synthetic or cultured DNA as the demand for them could not only lead to an increase in the demand for (illegal) natural specimens, but they could also be mixed with (illegal) natural specimens. The displacement of some of the natural products (i.e. naturally occurring molecules obtained from plants) can also potentially ease negative pressures on wild or cultivated species, but it can also displace cultivation practices, often in topical and sub-tropical regions."	Comment noted.
PRRI	08 and 9	44-48; 1-11	- Many aspects of regulation, policies, recommendations may be pertinent to the regulation of modern biotechnology, these can be expected at different levels and dealing with different overarching aspects including ethics and	Comment noted.

			may have to be addressed concurrently. - It is not true that current regulatory frameworks appear ill equipped to avoid unintended irreversible environmental damage… To date Synthetic Biology products are LMOs per definition and there is no documented evidence of damage caused by GMOs/LMOs. - It has not yet been concluded whether Synthetic Biology is a New and Emerging Issue. The AHTEG on Synthetic Biology concluded "that most living organisms already developed or currently under research and development through techniques of synthetic biology, including organisms containing engineered gene drives, fell under the definition of LMOs as per the Cartagena Protocol." If concrete examples fall outside the definition of LMOs, there are still several questions to be raised before deciding whether regulation is needed, when is needed, before deciding how to regulate. The whole part would gain credibility if rewritten in a more realistic way.	
Expert committees of DFG	09	03-11	This holds and is inherent for any economic or technological activity. It is unfounded to single out synthetic biology in this context.	Comment noted
GJSG on SynBio	09	03-11	This holds and is inherent for any economic or technological activity. It is unfounded to single out synthetic biology in this context.	Comment noted
JCVI	09	3-11	The unwarranted generalization of this closing paragraph of the executive summary contradicts the far more balanced previous page, which recognizes that applications of synthetic biology are many and varied and "cannot be generalized" (page 8, line 29). Nations focus their governance of most products on biosafety, human health, and the environment for good reasons. A few products may require a "more holistic approach" as described in the paragraph, but to generalize this to all applications that use the tools of synthetic biology is not at all justified by most of the examples discussed throughout the report or the quite comprehensive review of the technical literature.	Comment noted. Revision made
Global Industry Coalition	09	03-11	**Delete the entire paragraph, it is repetitive of previous content and unnecessary.** **Further, the first sentence (lines 3-6) contains generalisations and is misleading. The author's conclusion is not substantiated by the review**	Revision made.

			presented in this document. Rather, their review points to the fact that today views remain split on what synthetic biology is and what "novel" elements require new or expanded governance. **Furthermore, the last sentence (lines 8-11) implies that R&D is not conducted responsibly today. What evidence can be provided by the authors to substantiate this claim?**	
CDTBE-UK	09	06-07	Much environmental damage has already been done by other technologies. Synthetic biology can be a tool to undo this damage (e.g engineered cyanobacteria for CO2 absorption).	Revision made
ETC Group	09	07	It is good to calls for "integration with social sciences and engagement with communities", but this should be implented in this document. Yet the paper only cites examples of this being undertaken by the proponents of the technology (see General Comment 4).	Comment noted.
African Centre for Biodiversity	09	07	The reference to the need to integrate social sciences and engage with communities is good, but should feature more prominently throughout the document, particularly in terms of implementation, beyond promoters/developers of the technology.	Comment noted.
CDTBE-UK	09	08	First, there is a need to further educate communities in synthetic biology.	Revision made.
IWF	09	08	The section can be explained further on how awareness will be generated among communities.	Comment noted.
Global Industry Coalition	09	12	**Insert** "*hereinafter referred to as [**insert name of this document**]*"	Comment noted
Federation of German Scientists & ENSSER	09	14 onwards	General comment The headings of the Key Messages under the section of "current state of synthetic biology" - in particular messages 1, 2, 3 and 4 would benefit from adjusting, as they contain misleading claims, exaggerations and language that does not befit this report. The way it is presented portrays an over-enthusiasm for the technologies and a clear bias. It would be best to write	Revisions made

			new headings that are more fitting and neutral and factual in their presentation.	
CDTBE-UK	09	15	The "current state of synthetic biology" section could be accompanied by a subsection explaining the current situations that lead to the need for synthetic biology (i.e. environmental, health and social issues).	Comment noted. Key messages section has been restructured.
Federation of German Scientists & ENSSER	09	17	The heading reads: "Synthetic biology is a cross-cutting and rapidly advancing discipline that has gained great attention due to its increasing relevance to the environment, food and health among other global challenges." Firstly, this heading is the wrong kind of heading for the text that follows, as the text looks at what is considered synbio, its regulation, views about synbio and the challenges to consensus building. Secondly, this heading is a making a claim that is unsupportable, biased and misleading. Synbio has gained great attention not because of a supposed increasing relevance (in particular to the environment, food health and other global challenges), but because of its claims and promises, and the power of these claims and promises to capture the headlines and possibly minds. Sociologists argue, that underlying this is the desire to believe that technology can help us to continue with business-as-usual but avoid disaster.	Revision made.
Global Industry Coalition	09	27	The authors imply that there are products of synthetic biology that are not regulated ("… whether and how..."). We underline and remind the authors that while not all products may be captured for regulation under biotechnology or LMO provisions, they are nevertheless regulated by appropriate product and application specific regulatory provisions (e.g. chemicals, biologicals, etc.). We recommend that this point is considered throughout the text where claims are made that products/processes may not be regulated. It should not be implied that if something is not addressed directly by the CBD then it is not addressed at all, or it is addressed insufficiently elsewhere.	comment noted.

Expert committees of DFG	09	28	We do see reason to consider gene drives differently, because of their built-in/by-design capacity to propagate through populations. However, with the exception of such gene drives, there is little reason to consider synthetic biology differently from any classical GMOs.	comment noted.
GJSG on SynBio	09	28	Gene drives targeting disease vectors or invasive species are potentially harmful to biodiversity due to their capacity to propagate through populations. With the exemption of this application, products of gene-editing do not differ from other "conventional" GMOs.	comment noted.
Global Industry Coalition	09	28	**Replace** "*used with classical genetic engineering) albeit"* with "*currently used for biotechnology"*. **Insert** "or without" after "with".	Revision made
Federation of German Scientists & ENSSER	09	28	'albeit' - see comment page 8, line 33	Comment noted
Federation of German Scientists & ENSSER	09	28 & 29	'classical' - see comment page 8, line 32	Revisions made
Global Industry Coalition	09	29-30	**Replace** "*classical genetic engineering*" with "*genetic engineering in the 1970s*"	Revisions made
DER VBIO & GASB	09 (11)	31f	***"…. 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."*** That is certainly correct. In our understanding a specific risk assessment is necessary for each single product (see p56, c43). Keeping that in mind – due to the lack of a proper definition in this text – a wide range of methods and application will be covered; we doubt that this broad assessment approach will be feasible in practice and can meet the requirements adequately.	Comment noted.
Federation of German Scientists & ENSSER	09	32	After 'biodiversity related issues' ADD ",including human health"	Comment noted.
DER VBIO & GASB	09 (11)	34f	***"The potential of the synthetic biology toolbox is boundless, and so are the opportunities for synthetic biology to have an impact in an unprecedented***	Revision made

			manner." The potential of the synthetic biology toolbox is expanding - but it is certainly not "boundless". The impact of synthetic biology might be significant – but the impact of low-tech approaches can be even bigger. For example, the global use of concrete for construction, a low-tech product several centuries old, has increased dramatically over the last decades and we just experience in an "unprecedented manner" its impact on CO2 emissions and climate. *Ä We suggest rewriting the statement avoiding the terms "boundless" and "unprecedented"*	
Federation of German Scientists & ENSSER	09	34	Key Message 2: "The potential of the synthetic biology toolbox is boundless, and so are the opportunities for synthetic biology to have an impact in an unprecedented manner." As before, this is more befitting to a synbio press release or PR document than a technical CBD series. How is the potential of a toolbox boundless? And why or how are the opportunities to impact boundless, and what is implied by an "unprecedented manner" ? It is a heading full of superlatives offering little help for the tasks at hand, in particular when the reader is expecting to be given some actual information on the current state of synthetic biology. If you intend to keep the heading, please ADD "and risks" after 'opportunities' to give at least a hint of balance.	Revision made.
JCVI	09	34, 35	Hyperbole may make for more interesting reading but is less accurate. Synthetic biology's potential is not boundless, nor will its' impacts be unprecedented.	Revision made.
Global Industry Coalition	09	34-35	**Revise**. Speculative statements and exaggerations such as "*have an impact in an unprecedented manner*" , "*…the potential of synthetic biology toolbox is bondless*…" should be toned down.	Revision made.
Expert committees of DFG	09	34-49	This paragraph mixes, like many other parts of the document, approaches with potential to conserve biodiversity with gene-drive approaches that aim at	Comment noted.

			eliminating "unwanted" biodiversity. There is a fundamental difference between the fermentation-based biosynthesis of a natural product that avoids resourcing from natural, endangered populations, and the elimination of, e.g., disease vectors or invasive species.	
GJSG on SynBio	09	34-49	Gene-drives are special applications of gene-editing and cannot be regarded representative of all synthetic biology applications, as the text suggests. Synthetic biology allows for the production of pharmaceutically active natural products by engineered microorganisms – independent from natural sources (plants) and thus preserving valuable eco-systems and biodiversity.	Comment noted.
UK EBLC	09	34-49	See the introductory comments above – this section (2) does not provide an adequate risk-benefit analysis.	Comment noted.
Federation of German Scientists & ENSSER	09	36	When referring to the "numerous" applications that have reached the market please specify what they mostly are (e.g. flavours and fragrances, contained use applications, ...) to help focus the mind rather than being drawn to speculation.	Revision made
Global Industry Coalition	09	36-37	**Revise**. Some of the examples included in the list (Table 1) are not examples of synthetic biology but biotechnology. This needs to be underlined by the authors again in this part of the key messages.	The rationale could be consulted in S&M section.
Expert committees of DFG	**11** (actually page 9)	37-38	Some of these applications directly target global challenges such as climate change by for instance aiming at increasing the resilience of species to climate change (i.e. in corals),.. => Species with higher resilience to climate change should be excluded from SynBio; otherwise natural adaption and evolution would have to be included, too.	Editorial suggestions noted. The definition and scope of synthetic biology for the purpose of the Updated Technical Series is comprehensively addressed in Section B Scope and Methods.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	09	37-39	Tackling climate change by Synthetic Biology is a complex challenge, where virtually no projects are close to the market, and even research is limited. Here a realistic example should be identified to support the claim, as research and development to increase resilience of corals to climate change is in its	Revision made

			infancy and mostly hypothetical (c.f. IUCN 2019 Redford "genetic frontiers…" p.91)	
Federation of German Scientists & ENSSER	09	37-39	Please ADD "under development" after "Some of these applications". Please check (and clarify) if you mean that the applications suggested here are to address climate change itself or the impacts of climate change, i.e. here the effect of the warming of the ocean. When referring to climate change adaptation, the Corals example given is one where research is in its infancy and it should not be portrayed as if synbio can provide an answer. Please provide an example that does not rely on speculation. You may want to acknowledge however, that climate adaptation and resilience are mostly traits and capacities that grow out of interactions between systems and networks, and adjusting traits within one organism/species is highly complex.	Revision made
Expert committees of DFG	11	40-41	applications are also targeting the replacement of natural materials to take pressure of wild populations, as is the case of the production of recombinant Factor C (rFC) from synthetic horseshoe crab blood,.. => this is just recombinant technology / molecualr biology and not SynBio	Comment noted.
WHO	09	41	Horseshoe crab blood requirements in the context of the COVID-19 vaccine development could be mentioned here (and quantified later in the report).	Revision made.
CDTBE-UK	09	44	'Target species' which are usually vectors carrying pathogens that might be damaging for the environment (crops) or to society (humans)	Comment noted
Global Industry Coalition	09	46	**Replace** "*development*" with "*investigation*".	Revision made
JCVI	09	49	After an informative list of applications, the statement that these applications could have an impact in an unprecedented manner is not justified and is not accurate.	Revision made
WHO	09	49	Mostly repetition. Perhaps delete after word "application"	Comment noted

Federation of German Scientists & ENSSER	09	40-43	This sentence does not reflect the crucial nuances presented under section 4.4 which shows that there may also be serious drawbacks and previously unexpected (unpredictable) negative consequences with replacements of natural materials, such as rhino horn. (see also comments for page 47, line 28). Concerning squalene, whilst this substance was originally sourced from particular sharks, it has long since been obtained from plants, such as olives, and highlighting it here in this context is somewhat misleading.	Comment noted
PRRI	09	43-44	a diversity of gene drives is being studied and developed to control diseases and invasive pest populations that threaten biodiversity not only by suppressing the population but also by affecting the intrinsic capacity of the vector to host the disease agent (replacement/modification strategy). Examples of replacement strategy include an anti- schistosome gene drive in snails to control Schistosomiasis which is one of the most important and widespread neglected tropical diseases (Maier et al 2019. Gene drives for schistosomiasis transmission control. PLoS Negl Trop Dis. 2019 Dec 19;13(12):e0007833. doi: 10.1371/journal.pntd.0007833); and impairing the ability of female mosquitoes to transmit the Plasmodium parasites that cause malaria (Adolfi, A., et. Al 2020 Efficient population modification gene-drive rescue system in the malaria mosquito Anopheles stephensi. Nat Commun 11, 5553 (2020). https://doi.org/10.1038/s41467-020-19426-0)	Revision made.
PRRI	09	47-48	As the existing living products derived from Synthetic Biology fall into the definition of LMOs under the Cartagena Protocol they were submitted through RA&M in line with annex III of the CPB before placing in the market. There is no scientific evidence that products resulting from Synthetic Biology are having an impact in an unprecedent manner to biodiversity. Please explain specifically in which (positive and negative) ways products impact biodiversity compared to alternatives and give references.	Revision made
Global Industry Coalition	09	48-49	**Delete** " *These are only some of the many examples of synthetic biology applications that are having and could have an impact in an unprecedented manner*".	Revision made

			If the sentence is to be retained, the authors must substantiate their claim for "unprecedented manner" and provide examples of what exactly is "unprecedented" for such applications.	
Max Planck Institute for Terrestrial Microbiology	09		The use of gene drives is a very extreme example for genetic engineering and not exemplary for "synthetic biology". There is a tendency to use "gene drives" as an extreme example for a product. Per se the "product" and its consequences, but not the methodology that was used to create the product should be evaluated.	Comment noted
DER VBIO & GASB	10 (12)	1ff	***"The value of the synthetic biology market has increased exponentially."*** From the fact that the market for synthetic biology products has grown, a special need for action or regulation is derived. This is an unjustified linkage and not convincing. However, this section is particularly misleading and gives a wrong impression, as the definition of Synthetic Biology in this market analysis differs significantly from the topics addressed in this document. The markets and applications in the cited study focus on closed-system applications. These applications neither utilize biodiversity nor have any impact on biodiversity specific to synthetic biology, if already existing regulations are met.	Revision made.
Max Planck Institute for Terrestrial Microbiology	10, 16	1 ff, 26 ff	Most of the examples (or products) are rather considered classical GMOs and not "synthetic biology"	See scope and methods for clarity on scope and definition.
Western Michigan University	10	01	It should also be noted that there is significant effort developing synthetic biology applications that are not expected to have market value, but will be deployed in a not-for-profit way. These might not have a market value but will contribute significantly to economic productivity through the expected health benefits.	Revision made
Outreach Network for Gene Drive Research	10	01	It should be recognised that there is much ongoing work on non-profit applications of synthetic biology. They will not have market value per se but can support economic growth in other ways (e.g. through improved public health outcomes).	Revision made

Federation of German Scientists & ENSSER	10	01	Key Message 3: "The value of the synthetic biology market has increased exponentially" A few comments: a) It is not clear why this message is given under "current state of synthetic biology". b) I could not find any backup in this report for the claim that the synbio market has increased exponentially. For which period? Is it still doing so? Section 1, page 16, lines 17-21 merely state that the market "has experienced significant growth in the past decade". Please provide reliable data and sources to back up your statement of exponential growth between 2015 and 2021 or for whichever past period it is correct. c) If this is a key message it would be important to have a reciprocal extended section in the report, breaking down which aspects of the synbio market/industry are adding to which extent to the growth of the market, providing which products or services. Without such a section the key message appears to have little value and appears more promotional than evidence-based especially since the biggest claim is made about the future, ie: 2021-25.	Revision made.
GJSG on SynBio	10	01-09	Most of what is described here cannot be considered synthetic biology products	See scope and methods section
UK EBLC	10	01-09	This section (3) is misleading as it does not identify the key areas of industrial activity. The greatest products are proteins and enzymes produced in containment, such as chymotrypsin used in cheese production and washing powder enzymes used in laundry detergents. The scope and scale of this industry is enormous and synthetic biology has significantly increased its reach into flavours, fragrances, cosmetics, synthetic rubber etc. It is factually incorrect to say that it is being driven by synthetic DNA and nucleic acids, this is a niche research product. The reference to therapeutics and the CRISPR toolbox is also misleading here.	Revision made
EBRC	10	03	Suggest: "essential function of (engineered) genomes and biological systems"	Revision made

Imperial College London	10	04	There are many not-for profit research projects that develop engineered gene drives to provide potential solutions to challenges regarding public health and conservation.	Comment noted
Global Industry Coalition	10	06	**Revise**. Products "*produced in containment e.g. synthetic DNA, synthetic RNA, and oligonucleotides across various industries* are not "new" or "synthetic biology".	Comment noted
Federation of German Scientists & ENSSER	10	06	"products": whist on one hand being products, they are actually largely 'compounds' required for research, testing and services (examples given here are synthetic DNA, RNA, oligonucleotides). It would be helpful to differentiate between 'products' intended for the release on the market, and 'products' that are compounds for use within research and test providers (e.g. for diseases, presence of particular genes, detection of contamination etc).	Comment noted and revision made.
Federation of German Scientists & ENSSER	10	09	Why are technologies and techniques and capacities constantly portrayed as a "toolbox"? as here a CRISPR-toolbox? It gives the wrong tone and impression when dealing in fact with life-sciences and processes, many of them not fully known or predictable. They are therefore distinct from machines and mechanical processes.	Comment noted
Federation of German Scientists & ENSSER	10	10	Key Message 4: "Supporting technologies and tools have rapidly evolved, spawning even more types and numbers of applications, to the extent that synthetic biology is essentially ubiquitous in life science." Firstly, the choice of language is, as with other headings or key messages, problematic and evocative rather than factual, clear and helpful. In particular the term "spawning" "even more" is inappropriate, as it suggests technologies and tools being seen and taken as life and life giver itself. The sense that synthetic biology is now present in all of life sciences is very misleading, as much of it would be due to classic components of genetics research, such as sequencing. The use of nucleotide sequences to test for the presence of genes in populations via PCR is also not synthetic biology, but simply a methodology of modern genetics. By calling almost every approach used a technology of synthetic biology, then the term has lost use and meaning.	Comment noted. Revision made.

			Hence please differentiate and resist the further erosion of terms and concepts, thus making discussions and dialogues even harder. Secondly, and linked to this: it is not clear why there are only "supporting" technologies and tools, as it leaves unanswered the question: what are the actual technologies that are being used? When relating to section 1 (starting page 16) it would be important to differentiate between essential techniques or processes of synthetic biology and supporting technologies and processes, with the latter not being viewed as synthetic biology as such.	
Imperial College London	10	10-17	This complexity of areas suggests it is not one single discipline.	Revision made.
Global Industry Coalition	10	10-21	**Replace** "*supporting*" with "*enabling***"** technologies.	Revision made.
JCVI	10	19, 20	Plant synthetic biology is lagging behind bacteria and yeast, but not behind mammalian systems. As described later in the text, there is considerable activity, both in product development and development of new tools, for use in agricultural plants.	Comment noted.
DER VBIO & GASB	10 (12)	23	*„**Despite its potentially global deployment, research and development in synthetic biology mostly occurs in a limited number of countries "*** We agree that the potential of Synthetic Biology is not fully used by every country and that this gap needs to be filled. As a positive example, we want to name specifically the iGEM competition (https://igem.org/Main_Page), which helps greatly to disseminate Synthetic Biology around the globe. At the same time, however, we note that, in some countries, the total R&D in Synthetic Biology comes down to a single iGEM team made of university students. Whilst acknowledging the differences in structure and amount of funding, we would like to point out that the mentioned gaps often result from divergent political priority settings, too. Some countries could certainly put in more effort, both in terms of funding and policy, to support the deployment of Synthetic Biology in their country. However, the cited figures would be more convincing if comparative figures on the distribution of research funds and projects from other areas of the life	Comment noted.

			sciences were provided, as well as the total amount on funds spent for R&D projects. The figures seem to reflect the general disparity in research funding between countries, and more efforts towards technology dissemination and scientific collaboration are certainly needed. *Ä We suggest that the special funding asymmetry in the field of synthetic biology be supported by a comparison with corresponding key figures from the field of life science research. Furthermore, an overview of national funding strategies and roadmaps for synthetic biology could be helpful.*	
CDTBE-UK	10	23	Like with all new technologies, some leading/pioneer countries are the first ones to integrate it, but they are by no means the last.	Comment noted.
IWF	10	23	The technology need not to be limited to the leading countries in future.	Comment noted.
Federation of German Scientists & ENSSER	10	23	General comment Please see comments section 1 page 17, as that section is the basis for the text of the summary, and amend this section of the summary accordingly	Revision made
UK EBLC	10	23-34	The point about research and development taking place in a relatively small number of countries is true of all areas of scientific research and is not limited to synthetic biology. Indeed many aspects of synbio are seeking to democratise the science and address these inequalities. I myself have been involved with the development of low cost approaches and have been working with resource limited countries to improve education and science opportunities and capabilities.	comment noted.
Federation of German Scientists & ENSSER	10	25	It should be “by 2016” or “by end of 2015”, as Shapira et al. 2017 did their search between 2000-2015. Preferably it should say something like: “Between 2000 and 2015 some 8064 publications were identified linked to synthetic biology, including patent documents, indicating that more than	Revision made
Expert committees of DFG	10	26	Why was the timeframe starting with 1980 considered? 1980 is the time when classical genetic engineering became possible. Synthetic biology as a	Revision made

			recognized discipline in life sciences can be dated to the beginning of the 2000s, although the term has been (rarely) used before.	
GJSG on SynBio	10	26	Synthetic biology has been recognized as a discipline in life sciences since the turn of the century.	Revision made.
Federation of German Scientists & ENSSER	10	26	It is incorrect to say "since 1980", as the term and concept of synthetic biology were not around then. Equating it simply with Genetic Engineering would not be helpful. Please check and clarify.	Revision made.
Federation of German Scientists & ENSSER	10	29	"the authors reported" - it is not clear who is being referred to here.	Revision made.
Global Industry Coalition	10	30-31	**Revise**. It would be informative to note how many of these global sponsors are public funding bodies.	Revision made.
UK EBLC	10	37	This ignores the enormous industrial activity highlight in the comment to message 3 above. People have been interacting with and eating the products of synthetic biology for decades. Synthetic biology is not as new or as radical as this seeks point seeks to make it.	Comment noted.
Federation of German Scientists & ENSSER	10	37	Key Message 6: "Synthetic biology products designed for use in managed, semi-managed and urban situations attract the greatest attention as those are the ones that the public at large will have greatest interactions with." This is the beginning of the new subsection 'Potential impacts from synthetic biology'. It is not clear at all how this heading is related to potential impacts. It is also not clear whose attention is being attracted here? Policy makers? Press? Funders? Risk assessors? It might be more helpful to say that LMOs produced through synthetic biology are about to move out of the lab into the field (if that is what the authors of this draft have found and want to say here). Yet neither of such headings however reflect what is covered in the text that follows.	Comment noted. Revision made.

JCVI	10	37-39	While the text of the paragraph below is informative, the title is neither accurate or a summary of the paragraph itself. The public at large will have greatest interactions with products from contained settings. Those that have attracted greatest attention are those intended for wild settings, even though they are in the earliest stages of development. The title should just describe that organisms modified using the tools of synthetic biology are varied, with most intended for use in contained settings, followed by those intended for managed settings, and a few for wild settings.	Revision was made
Federation of German Scientists & ENSSER	10	40	"Synthetic biology has provided an unprecedented toolbox for tailoring organisms for new applications and products." If this section is meant to cover impacts, and it starts with "tailoring" organisms for new applications, a clear impact seems to be that organisms are no longer perceived as part of ecosystems and having a standing on their own, but rather as something that one tools and tailors according to perceived wishes and requirements. This is deeply concerning, as it depicts the lack of recognition and thorough understanding of the complexity of living systems, including ecosystems, and their interactions and interdependence. However, given this is going to be a document under the CBD, and the CBD has a long history of understanding ecosystems and of working towards the conservation and sustainable use of biodiversity, this introductory sentence should be rephrased, to place synthetic biology within the context that the CBD has debated for the last 8 years. As often reiterated at CBD meetings and also recognised at IPBES there are different kinds of knowledge systems, including western science; the knowledge held by Indigenous Peoples and local communities and peasant farmers is deeply interconnected with their local ecosystems and must be respected. This is one of the particular aspects of the CBD, that it seeks to do so. As discussed and acknowledged by the AHTEG on synthetic biology, this knowledge is of a very different nature to that connected with synthetic biology.	Comment noted. Revision made.

PRRI	10	42-45	Genome editing are a set of tools and techniques not exclusive to Synthetic Biology. They can be used in many ways such as in precision breeding/New breeding Techniques and on usual modern biotechnology. It is wrong to consider the use of the set of tools like genome editing as an indication of any specific technology branch. To our knowledge the LMO self-limiting insect is not yet commercialized. Please give references.	The references are provided in the main text, not in the Executive Summary
ISF	10	43-45	Examples of simple genome edited crops are reference here and in table 1 on page 13/14 as synthetic biology. Please revise! Targeted introduction of mutations through genome editing is not synthetic biology! Examples referring to simple genome edited crop plants need to be removed.	See scope and methods for clarity on definition and scope.
GJSG on SynBio	10	44	Genome-edited crops are not products of synthetic biology.	See scope and methods section
Expert committees of DFG	10	44-45	It is unfounded to classify the genome-edited crops mentioned as products of synthetic biology? Following lines – it is misleading to repeatedly mention genome-editing in the context of gene drives. While genome editing can be applied to build gene drives, the vast majority of genome editing events are targeted mutagenesis, not gene drives. It would make sense to consider gene editing throughout this document only if it is applied to generate gene drives.	See scope and methods for clarity on definition and scope.
Global Industry Coalition	10	44-45	**Revise**. The genome editing crops and self-limiting insects are not examples of synthetic biology. Why are such examples now assigned as synthetic biology?	See scope and methods for clarity on definition and scope.
GJSG on SynBio	10	45	Genome editing serves for targeted mutagenesis, gene drives is only a very small niche application.	Comment noted
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	10	45	Self-limiting insects (also p.31 line 27 ff) were developed by Oxitec and are tested in the environment. To our understanding those products are not marketed commercially but are still in testing phase.	Revision made
Federation of German Scientists & ENSSER	10	45	If this refers to the Oxitec RIDL mosquitoes or insects, we consider these to be still at the testing stage (see comments later)	Revision made

ZKBS	10	46	The sentence “It is expected that some other genome edited organisms and potentially those containing engineered gene drives could reach the market in a few years.” implies that organisms containing engineered gene drives are genome edited. However, to cause a gene drive, a substantial, genetically complex insertion into the genome of an organism is needed. This is not what is usually understood by “genome editing” where only small insertions/deletions or changes of a few nucleotides are made. The sentence should be changed to: “It is expected that some other genome edited organisms and ~~potentially those~~ *organisms* containing engineered gene drives could reach the market in a few years”. Again, the ZKBS would like to strengthen that “gene drives” are not per se an item of synthetic biology.	Revision made
Federation of German Scientists & -ENSSER	10	46-47	We consider engineered gene drives to also belong to the category of unmanaged and wild settings and not to be limited or limitable to managed or urban settings.	Some gene drives applications are intended to unmanaged settings, while others in semi-managed settings. See sections 3.1 and 3.2.
Western Michigan University	10	47	Define the use of the word "market". The gene drive applications currently under development are not going to be commercially distributed. In particular, the gene drive applications listed in Table 1, for the control of vector-borne diseases, will not be marketed, but will be deployed by governments or regional bodies as part of a public health campaign. Furthermore, the status of the gene drive research should not be classified as in the advanced stages. There have been no field trials of such synthetic biology developments, and therefore they are quite early in the developmental pathway.	Revision made.
Outreach Network for Gene Drive Research	10	47	Saying that “gene drives could reach the market in a few years” is potentially misleading, as the most advanced gene drive applications currently under development will not be sold or distributed on a commercial basis and are still far from being ‘ready for use. They are intended to complement public vector-control campaigns or public invasive alien species control campaigns.	Revision made

Imperial College London	10	47	Current engineered gene drives in development are not for profit and will not be commercially sold.	Revision made
Global Industry Coalition	10	47	**Replace** "*reach the market*" with "*be deployed*". The gene drive applications currently being developed will not be marketed.	Revision made
Federation of German Scientists & ENSSER	10	51	this sentence does not make sense. Also there seems to be too much emphasis on interactions between people and these applications	Revision made
Expert committees of DFG	10	44205	Most of what is described here cannot be considered synthetic biology products	See scope and methods for clarity on definition and scope.
Federation of German Scientists & ENSSER	10	General comment	The text does not give any details relevant to the section title *'Potential impacts from synthetic biology*'. It merely lists the state of play and of development, which would be more suitable for the previous section. Another problem is that the piece does not seem to recognise - or fails to portray - the difference between a laboratory setting and an ecosystem: in the former there is more possibility for control than in the latter. There is much we do not understand about the interactions within ecosystems and we have to accept this, not imagine we can overcome it with the correct tools or tailoring.	General comment noted. Revisions made.
WHO	10	Key message 5	The 2017 figure could perhaps be updated. Further consideration should be given as to how representative such a figure is. For example, much of the Chinese language scientific literature is not reflected in standard global scientific databases. Scope and extent to which the targeted research and relevant literature are captured should be further considered within the context of key identified limitations. The patent documentation at national, regional and global levels could suggest that the figures provided underestimate the scale and scope of application of synthetic biology. The role of industrial secrets and classified government work could be further considered in terms of methodological limitations.	Comment noted.
Federation of German Scientists & ENSSER	11	01	I suggest to ADD "or release" after 'for direct use'	Editorial suggestion noted.

CDTBE-UK	11	01-10	The argument that Synthetic Biology should be regulated similarly to GMOS due to the lack of data of commercialised products is very vague.	Comment noted.
UK EBLC	11	01-10	This section (7) is simply untrue and unfounded. GMOs can be considered as early products of synthetic biology. They have now been used in the environment for nearly 3 decades and as of 2013 there were 432 million acres under cultivation (ISAAA 2013 Annual Report Executive Summary, Global Status of Commercialized Biotech/GM Crops: 2013 ISAAA Brief 46-2013). Further, these crops were based on extensive testing of lab and field based trials, so is extensive experience of taking products from the lab into the real world. The argument that Synthetic Biology should be regulated similarly to GMOS due to the lack of data of commercialised products is very vague. Indeed, extensive assessment of this issue has been devoted by regulators globally, leading to clear delineation between GE and GMO regulatory spaces. Only within Europe has the balance been determined upon legal and not technical considerations, a position that has been strongly challenged by the scientific community.	Comment noted.
CDTBE-UK	11	02	Potential impacts that have been studied in a laboratory context can already provide a lot of information, making our understanding not merely a hypothesis or speculation.	Revision made.
IWF	11	02	More dataset will be need to make a conclusive argument.	Comment noted.
Federation of German Scientists & ENSSER	11	04	This should clarify that it is the impacts of 'synthetic biology applications (LMOs and products) released into the environment' on the conservation and sustainable use .... This is important, as the impacts on conservation and sustainable use from synbio products that are marketed to replace natural products is possible to monitor and assess already. In fact it should have started as a matter of urgent inquiry once marketing started to assess the consequences on livelihoods and conservation and sustainable use of biodiversity. Moreover, there is no mention of the application of the precautionary principle here, which is	Comment noted. Revision made.

			fundamental to the CBD and could point towards conclusions that can already be drawn BEFORE any release has taken place. Please attempt to adjust.	
Western Michigan University	11	05	Replace “largely” with "entirely". No data are so far available on the impacts of these applications on the conservation and sustainable use of biodiversity. If the authors are aware of any studies, they should be reviewed in this document, since they would be key examples to note, and then “largely” can be used.	Editorial suggestion noted.
Imperial College London	11	05	If it is largely hypothetical there should be examples listed which application has affected biodiversity.	Comment noted. Revision made.
IWF	11	06	More dataset will be need to make a conclusive argument.	Comment noted.
JCVI	11	06-08	I think the sentence on p.9, lines 29-31 is more accurate. Rather than being informed by actual experience with LMOs, the current debate just echoes concerns expressed at the emergence of classical genetic engineering.	Comment noted. Revision made.
Federation of German Scientists & ENSSER	11	06-10	More time and experience will be needed before decisions on this point can be made. There should not be a rush but rather a time for investigation and detailed observation to gather sufficient data for future decision-making on this matter.	Comment noted.
Western Michigan University	11	07	In the same vein as the previous comment, this should be "entirely"?	Editorial suggestion noted.
CDTBE-UK	11	08	As well as with experiments carried out in a lab which can provide a huge amount of information on potential impacts.	Comment noted. Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	11	08-10	The message of this conclusion is unclear. I propose to replace it with: “It might be too early to be able to conclude on potential impacts associated of most SynBio applications.”	Editorial suggestion noted. Revision made.

CDTBE-UK	11	11-26	You could argue the same when civilization moved from an agricultural economy to a more industrialised one. Sometimes practices complemented each other rather than replacing each other.	Comment noted. Key messages section has been restructured.
Expert committees of DFG	11	11-26	Any regular crop, animal introduced, i.e. any human activity leads to this. There is no need to regulate synthetic biology any differently. In turn, the organism as in synbio applications has modifications perfectly tractable, are thoroughly described, with a tighter control being possible	Comment noted. Key messages section has been restructured.
GJSG on SynBio	11	11-26	This is a general effect of any human interference with ecosystems (e.g. introduction of novel crops or livestock). Why regulate synthetic biology any differently? In contrast, the modifications of engineered organism are perfectly tractable, thoroughly described, and allow for efficient control.	Comment noted.
UK EBLC	11	11-26	The first sentence of this section (8) cannot be meaningfully understood without more context. Some of this emerges further down the paragraph. However, it points to arguments that are wholly unrelated to the science. Similar concerns can be raised with regard to many other technologies, as they indeed have done throughout history. For instance, driverless cars will displace millions of jobs. While these concerns are real, they are questions of economics and policy and have no bearing on the safety and biodiversity considerations of the science and technology under discussion. Indeed they could just as easily be considered an opportunity for local management of land use and resource prioritisation. For instance replacing palm oil plantations by synthetic production of palm oil could have tremendous ecological benefits. The implications as currently framed are all taken as a negative context for the technology.	Comment noted. Key messages section has been restructured.
PRRI	11	11-26	The whole paragraph is speculative showing only possible negative effects of the replacement of natural products with products resulting from synthetic biology. Some commercially available products are unsustainably harvested from the wild and are pushing some species towards extinction. The development of alternatives could save some species. While there is no such replacement of natural products with products derived from synthetic	Comment noted. Key messages section has been restructured.

			biology, other experiences throughout history can be useful. For instance, the availability of a chemically synthetised the red dye alternative helped the otherwise overexploited and decimated brazilwood population used to extract a natural red dye precursor.	
Global Industry Coalition	11	11-26	**Revise** to make more factual. This section does not contain examples of experience so the title should be amended to reflect this. This paragraph is also biased. Its perspective/assumption is that traditional or smallholder cultivation practices are sustainable/ethical and moral/free of human rights and environmental abuses. This is a significant simplification that overlooks real life "nuances".	Comment noted. Key messages section has been restructured.
Western Michigan University	11	12	This section does not describe any experience, and therefore should not be titled as such. The discussion here lays out more nuanced speculations, not experiences.	Comment noted. Revision made
IWF	11	12	Examples should be mentioned of the experiences.	Comment noted. For example, specific cases are cited in Sections 4.4 and 5.2.2.
Global Industry Coalition	11	14-15	**Revise** for factualness. There is a suggestion that products of synthetic biology "*could also disrupt in situ conservation projects*" – please provide evidence for the demonstration of this.	Comment noted.
Federation of German Scientists & ENSSER	11	14-15	ALTERATION: Please consider the following bold additions to the first sentence: For example, the replacement of natural products with products resulting from synthetic biology could in some cases possibly lessen the pressure on natural habitats and specific species but could also disrupt or undermine in situ conservation projects.	Editorial suggestion noted.
Federation of German Scientists & ENSSER	11	16	Please define 'specimen' in this context	Comment noted. Revision made.
Federation of German Scientists & ENSSER	11	19	ADD : ....molecules **and compounds**	Editorial suggestion noted and revision made.

Expert committees of DFG	11	20	Typo, should read “tropical” not “topical”	Editorial suggestions noted and revisions made.
Federation of German Scientists & ENSSER	11	20	ADD: ... practices **and livelihoods**	Editorial suggestion noted and revision made.
Federation of German Scientists & ENSSER	11	21	DELETE: , this ~~therefore~~ may bring	Editorial suggestions noted and revision made.
CDTBE-UK	11	23	This also happens when bringing in non-native species. It is not an issue specific to synthetic biology, but of agriculture in a globalised world.	Comment noted.
IWF	11	23	The non-native species will interact in the same way, so its not specific to synthetic biology	Comment noted.
Imperial College London	11	23	Sentence incomplete	Comment noted. Message has since been revised.
Expert committees of DFG	11	24	“complex web of potential interactions” is not specifically inherent to SynBio applications; it is rather a generic aspect of any economic activity. Should hence not be considered in the context of SynBio but rather is an aspect of international trade laws	Comment noted. Revision made.
GJSG on SynBio	11	24	The “complex web of potential interactions” is not exclusively typical of synthetic biology – it rather is a definition of any economic activity,	Comment noted. Revision made.
CDTBE-UK	11	26	These paragraphs say that there could be complex and negative impacts, but not a specific case is given (specific technology in specific region).	Comment noted. Specific cases are cited in Sections 4.4 and 5.2.2.
IWF	11	26	To make the argument more conclusive there should be a section of case study pn the topic.	Comment noted. Specific cases are cited in Sections 4.4 and 5.2.2.
DER VBIO & GASB	11(13)	28ff	***Communication, engagement and transparency*** We recognize the need for early involvement of stakeholders and transparency. And, as scientists, we have to acknowledge that societal expectations can change and do not always harmonize with our views. However, what we do expect is a fair and open dialogue based on scientific	Revision made.

			facts and mutual respect. Issues of biosecurity and dual use certainly must be considered in overall regulation as well as in communication. However, there must be differentiation according to their impact level - e. g. for gene editing versus gene drives. Such differences should be communicated more clearly, and the paper CBD Technical Series No. 82, with its general lack of differentiation, does not reflect this demand. *Ä We suggest addressing the question of a fact-based dialogue and the necessary preconditions for a mutually respectful dialogue. It may be worth keeping in mind that according to the possible impact of the methods and approaches of synthetic biology different approaches of communication might be desirable.*	
Federation of German Scientists & ENSSER	11	29	Key message 9 - General comment - This section lacks a reflection on deliberative process, which is a helpful and promising approach when trying to understand problems and find solutions. This section would also benefit from adding the much discussed public concern of "need", and the assessment of need, so that the issue is not solely limited to safety measures and policy but also to defining needs and solutions.	Comment noted. Key messages section has been restructured.
UK EBLC	11	29-40	It should be noted that the synthetic biology research community has been actively engaged with outreach and leading the integration of Responsible Research and Innovation with funding and development frameworks. See comments below re conclusions section p131	Revision made.
PRRI	11	29-40	There is no reason to assume that products derived from Synthetic Biology are most likely to impact local communities and IPLCs first. Some specific examples may – positive or negatively - affect IPLCs and local communities depending on how they are used, where they are released, etc.	Revision made
Global Industry Coalition	11	30	**Revise** for factualness. Why are LCs most likely to be impacted first? This is another example of the authors making biased and broad assumption.	Revision made

JCVI	11	30-34	This paragraph again strays into the territory of sweeping generalizations. While IPLCs will be affected by some products of synthetic biology, for most products there is no reason to believe that they are "most likely to be impacted first" (line 31), thus no compelling reason why early engagement with IPLCs should be singled out. If this paragraph is about natural products such as vanillin (as discussed in the preceding point 8) or gene drives, be specific.	Editorial suggestion noted.
Global Industry Coalition	11	32	**Replace** "*construction*" with "*development*".	Editorial suggestion noted.
Global Industry Coalition	11	35-36	**Revise** for factualness. The text "*improve public trust through the development of safety measures and policies*" misleadingly implies that this is not the case already.	Editorial suggestion noted. Revision made.
EBRC	11-12	Message 10	How would this work in practice for contained industrial biotech products of synthetic biology (e.g. squalene) for global product applications? How realistic is it to involve all potential stakeholders a priori? How to balance Transparency for Consensus vs Confidentiality for competitive Innovation?	Comment noted. Revision made.
CDTBE-UK	11	42-51	Public engagement is crucial, but also the opinion of scientists and experts working in the field.	Comment noted and revision made.
UK EBLC	11	42-51	In the UK Responsible Research and Innovation is integrated into the funding process. (see comments and reference re p131)	Comment noted.
JCVI	11, 12	42-51, 1-7	Again, a sweeping generalization. The paragraph implies, and line 49 states, that any product made with synthetic biology somehow requires greater public engagement in regulatory decision-making. Please identify the type of products for which you are recommending this type of enhanced engagement.	Comment noted and revision made.
PRRI	11-12	42-07	Adequate public understanding and engagement is important part of the decision making on several topics of public interest. Yet informed decisions must take into consideration scientific knowledge especially in areas of high technical complexity.	Comment noted. Revision made.

			The covid crisis has shown the need rethink rulemaking to be more agile to harness the opportunities of innovation responsiveness in changing environments. There are discussions on how to better regulate emerging technologies on other spheres for instance OECD that it would be interesting to consider.	
Federation of German Scientists & ENSSER	11	51	ADD: of environmental and security concerns **and needs**,	Editorial suggestion noted and revision made.
Federation of German Scientists & ENSSER	12	04	ADD: ..importance of participatory **and deliberative** decision making	Editorial suggestion noted.
CDTBE-UK	12	07	While it's crucial to understand the public opinion in a community, this community needs to be well informed and educated on the topic. Due to the fast spread of inaccurate information, the general public may not always be in the best position to decide on such technical matters.	Comment noted.
EBRC	12-13	Message 11-13	Same remark as for message 10	Comment noted. Revision made.
UK EBLC	12	08-23	Biosecurity is tremendously important and it should also be noted that the synthetic biology community has also been at the leading edge of educating researchers in these aspects of RRI, and sponsoring workshops to ensure dur consideration has been given to this aspect	Comment noted.
PRRI	12	08-23	Important to include that the issue of dual use research and biosecurity measures are addressed by other instruments such as the Biological and Toxin Weapons Convention (BTWC) and the Chemical Weapons Convention (CWC). Other responsible measures for responsible research and innovation exist and should be considered. Safety is not served by overlapping systems.	Comment noted. These are covered more fully in Sections 5.4. (dual-use), 7.3 (self-regulation). & 9.3.1(b) (Biological Weapons Convention).
Third World Network	12	08-23	Biosecurity risks section has omitted the role of state actors. This section thus fails to acknowledge the substantial role of military funding for synthetic biology products such as gene drives, new projects to engineer skin microbiomes for repelling mosquitoes for US military personnel, HEGAA's or self-spreading vaccines for mammalian disease vectors.	Comment noted. Revision made.

			This section must thus accurately reflect the state of R&D including the actors involved that is rightly acknowledged in the main body of the text.	
ZKBS	12	08-23	1. The dual-use discussion is not inherent to synthetic biology. For example, dual-use concerns are discussed for genetic engineering as well. This is more likely a topic for the Cartagena Protocol or a general topic for the CBD. 2. Do-it-yourself biology is not an issue of synthetic biology and usually uses standard methods of genetic engineering leading to the creation of LMOs.	Revision made.
Federation of German Scientists & ENSSER	12	10	COMMENT: it should not only be with regards to intentional misuse but also unintended.	Comment noted.
Federation of German Scientists & ENSSER	12	11	ADD: ... public health, **environmental integrity, food production, livelihoods** and/or	Editorial suggestion noted. Revision made.
GJSG on SynBio	12	12-15	Compliance with biosecurity guidelines and expertise in biosafety and biocontainment practices must be demanded from professional scientists and amateurs.	Comment noted.
Global Industry Coalition	12	12-15	**Delete** the two sentences "*The "DIY Bio" community in particular has raised concerns … low tech laboratory settings"* These are problematic because they incorrectly suggest that the DIY community itself has raised these concerns, rather than the DIY community being the subject of these concerns. But more importantly, the relevance of these two sentences is not clear given that these concerns have been allayed by evidence of their actual activities, capabilities, and proactive approach to biosafety and biosecurity, which are discussed in this document.	Comment noted. Revision made.
Expert committees of DFG	12	12-16	Synthetic biology relies on a suite of supporting technologies and tools that enable the engineering and creation of biological components. These tools could include DNA synthesis, directed evolution, genome editing, engineered gene drives, RNA interference, artificial intelligence, machine learning, biofoundries, and BioBricks. Synthetic biology also covers several areas of research such as nucleic acid-based circuits, protein engineering, metabolic	Comment noted.

			pathway engineering, genome level engineering, protocell construction, xenobiology, and cell-free systems. => This "definition" is vague and not specific. It is essential to distinguish between synthetic biology being performed in research facilities by experts from amateur endeavours. The following of biosecurity guidelines, knowledge, equipment, infrastructure and necessary and documented expertise in biosafety and biocontainment practices and regulations must be complied. See also Section 5.	
African Centre for Biodiversity	12	18-23	This section needs to be revised to cater for the role of state actors, and specifically in the substantial and well documented role of state military funding for products of synthetic biology, such as gene drives, amongst others. This section must be revised to accurately reflect the current state of research and development, including from state actors, that is rightly acknowledged in the main body of the text.	Comment noted and revision made.
Federation of German Scientists & ENSSER	12	20	Self-regulation should not be an option. We need obligatory rules, as it is a matter of public safety and possibly national importance. Biosecurity issue and dual –use are far too important to be left to the researcher to highlight; furthermore the problems may not be immediately evident but emerging gradually.	Comment noted.
Global Industry Coalition	12	22	**Add the sentence at the end of the paragraph "Self-regulation through e.g. bioC399:E410safety and biosecurity education or interviewing (new) participants is also very prominently practiced in the "DIY Bio" community and iGEM initiatives, thereby responding to the concerns raised regarding lack of oversight or containment in these low tech (community) laboratory settings."**	Editorial suggestion noted.
CDTBE-UK	12	23	Half sentence randomly inserted	Editorial suggestions noted and revisions made.
JCVI	12	23	First part of sentence missing.	Editorial suggestions noted and revisions made.

Western Michigan University	12	23	Delete this sentence fragment.	Editorial suggestions noted and revisions made.
IWF	12	23	Errored sentence	Editorial suggestions noted and revisions made.
Global Industry Coalition	12	23	**Delete** "*of those countries form the basis of discussions aimed at reaching a consensus at the international level*".	Editorial suggestions noted and revisions made.
Federation of German Scientists & ENSSER	12	23	DELETE rogue ;) sentence: there is a problem here – only part of a sentence appears.	Editorial suggestions noted and revisions made.
WHO	12	Key message 12	Perhaps consider ISO standards, CEN regulations, information on the Belgian Biosafety Server (e.g. for assessment tools, reporting requirements, best practices, GMOs). See https://www.biosafety.be/	Comment noted.
Federation of German Scientists & ENSSER	12	27 & General comment	Key Message 12: "For synthetic biology to live up to its perceived (by whom?) potential, an enabling (for whom?) policy and regulatory environment is needed." This portrays an assumption that synthetic biology is desirable and should be facilitated as much as possible, without saying why or adding other views in balance. This is not a CBD issue. The precautionary principle offers sufficient guidance for the development of innovations. More importantly there should be an enabling environment for deliberative public processes with decision-making powers that will guide policies and force action to remedy and stop underlying causes that continue to worsen current crisis and to find real and long-term solutions, including change of practices and type of interventions. A technical solution approach is very limited in its reach and possibilities.	Comment noted.
UK EBLC	12	27-38	The effectiveness of the current regulatory environment should not be ignored here. I am not sure that a new paradigm is entirely required, but we do need to create an enabling rather than an inhibitory environment. This	Comment noted and revision made.

			section must stress the potential benefits and the RISK OF DOING NOTHING.	
Global Industry Coalition	12	32	**Delete** "*this century*".	Editorial suggestions noted and revisions made.
Imperial College London	12	34	Indeed, so far risk assessments under the precautionary principle tend to not include benefits.	Comment noted.
Max Planck Institute for Terrestrial Microbiology	14 (actually 12)	34 ff	*Often, international and national regulatory regimes tend to focus on biosafety risks rather than a more holistic approach 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. In this sense, a new paradigm for regulating synthetic biology applications is needed that looks beyond just biosafety*" It should be cautioned against bringing broader policy and societal issues into regulatory issues related to synthetic biology in the CBD. A more pragmatic way forward is an evidence-based approach, including evidence-based decision-making by the scientific community on a case-by-case basis to avoid violating biodiversity and sustainability goals.	Comment noted.
Western Michigan University	12	34-38	This is a key statement. To date, the application of a precautionary approach has tended to discount any benefits in the risk assessment and decision-making equation. These sentences signal that a re-interpretation of the precautionary approach might be necessary. Please consider stating this more explicitly in the document.	Comment noted.
PRRI	12	34-38	This statement needs a fact-checking, there are different laws, regulations, international instruments, policies, guidance, etc. that are applicable and cover different aspects beyond safety including ethics, consumers rights, etc.	Comment noted.
Global Industry Coalition	12	34-38	**Revise** for factualness. The paragraph provides assumptions without considering real life "nuances". Decision making processes under biotech regulatory systems take into consideration whatever issues are appropriate	Comment noted and revision made.

			according to national circumstances and priorities. A conclusion of there being a need for a "new paradigm" can hardly be justified - more than a decade of discussion on the topic under the CBD has not come to this conclusion.	
Federation of German Scientists & ENSSER	12	36	REPLACE: applications ~~is~~ **would be** needed This whole issue needs much further discussion and is not mature enough to be covered here in this angle.	Editorial suggestion noted.
JCVI	12	37, 38	Again, I see no justification for the recommendation that a new paradigm is needed for regulating products of synthetic biology. This may be the authors' policy preference, but it is not a conclusion that has been justified in the document. If the authors are referring to particular types of products, please be specific.	Comment noted and revision made.
PRRI	12	40-45	It is difficult to estimate on the basis of the number of research publications or investments whether an emerging technology will bring a challenging number of realistic and practical applications to the existing regulatory systems. Some horizon scanning for the developments on synthetic biology that may become reality within the next 20 years include: '- in 2017 New horizon-scan paper for synthetic biology and bioengineering https://www.cser.ac.uk/news/new-horizon-scan-paper/ gives a hint of sectors of relevance; - The "Horizon Scan of Synthetic Biology Developments for Microorganisms with application in the Agri-Food Sector searched for Synthetic Biology developments moving towards practical applications in the next decade, - https://efsa.onlinelibrary.wiley.com/doi/pdfdirect/10.2903/sp.efsa.2020.EN-1664" and identified using a search strategy including scientific publications and grey literature, websites demonstrating commercial activities in synthetic biology, databases of regulatory agencies and iGEM projects 10.000 items available during the period 2014-2018 from these Five cases fully passed all the inclusion criteria. - Other horizon scanning activities include: Horizon Scanning Series - Synthetic Biology in Australia: An outlook to 2030 https://acola.org/hs3-	Comment noted. Revision made.

			synthetic-biology- australia/ - Etc.	
Global Industry Coalition	12	40-45	**Revise** for factualness. Another real-life nuance here is that developers typically engage regulators early. The gene drive scientific community provide an example of this.	Comment noted. Revision made.
CDTBE-UK	12	41	'keep-up' not 'cope-up'	Revisions made.
IWF	12	41	The term keep-up can be modified.	Revisions made.
Global Industry Coalition	12	42	**Revise** for factualness. What is the "*fast pace*" referring to? The CBD discussions have been talking about a "fast pace" for more than a decade and still there are few commercial products outside of contained uses, and the products cited are not "synthetic biology".	Comment noted.
Federation of German Scientists & ENSSER	12	42 onward	Include 'horizon scanning'	Comment noted. Revision made.
UK EBLC	12	47-50	Synthetic biology is and should be viewed as a continuum from early genetic engineering in the 1970s. Indeed, it can be argued that the first true synthetic biology product was human insulin manufactured from engineered E. coli from a chemically synthesised gene. It is thus reaching a degree of maturity as it has now been going for nearly 50 years. The scope and scale has indeed radically changed, but this scope and scale addresses the degree of technical know-how, data input and output. This increase in capability is actually aimed at increasing the precision of what is being done, so that the output is both more predictable and more reliable than with less sophisticated efforts. This increase in precision must be contrasted to the non-specific methods of biological development that were used in the past and in fact in many cases are still being used. Plant breeding induces non-specific and widespread genetic changes. Non-conventional plant breeding methods enable the mating of plants that could not occur naturally, the induced genetic changes are inherently unpredictable and non-specific. Similarly mutation methods for the development of plant varietals are widely used and more than 2000 crop	Revision made.

			variants in use today were isolated by such methods. Again, these methods are untargeted and the changes are unpredictable and non-specific. Surprisingly therefore, the products of both of these methods are not subject to rigorous safety evaluation but are considered 'natural'. The scope and scale argument therefore does not support a definitive requirement for more regulation, the focus should be on precision, specificity and scope for unintended consequences. Such a perspective might raise significant questions over approaches that are currently considered natural. There are extensive existing safety laws for synthetic biology that are covered by a wide variety of regulations depending on the organism being used and the application environment. There are very few synthetic biology developments that need to be considered as a radical departure. Gene drives may be considered one such example, but as highlighted in point 13, these have been widely signalled through granting bodies, journal articles, conferences etc. Those working in this field are actively engaged in responsible research and innovation and this can in many regards be considered a model for how to approach technology with far reaching implications.	
PRRI	12-13	47-07	This paragraph is makes several unsubstantiated assumptions, there is no intrinsic need of creating a regulation only because a term is more used now than when the regulations were developed. In fact, several countries are actively reviewing which cases and how to deal with the advances of biotechnologies including synthetic biology.	Comment noted.
ZKBS	12-13	47-7	1. The document states under point 14 that synthetic biology is a new discipline. This is not agreed upon by all CBD Parties and other stakeholders. In dec. 13/17, it was concluded "that living organisms developed through current applications of synthetic biology, or that are currently in the early stages of research and development, are similar to living modified organisms as defined in the Cartagena Protocol;". Several Parties have the opinion that synthetic biology is a new kind of modern biotechnology and that regulatory mechanisms in place for living modified organisms are adequate to address synthetic biology. Point 14. needs to be rephrased accordingly.	Comments noted. Revision made.

			2. A regular monitoring of the scientific progress in synthetic biology would be adequate to identify necessary adjustments of national and international regulation. The German ZKBS has been carrying out such a monitoring, including a risk assessment of the applications identified, for almost 10 years (see https://www.zkbs-online.de/ZKBS/EN/Home/home_node.html à Synthetic Biology). It should be added to the text that a perpetual horizon scanning process is already established nationally in Germany.	
UK EBLC	12	48	This is not a foregone conclusion. The basic principles set out in the past generally do not change radically. With regard to specific technical advancements, regulations will need to be updated as appropriate. The default issue is generally that outdated regulations pose a blocker to progress, whilst new evidence and understanding is as likely to decrease the perceived risk relative to an earlier state of unknowing or uncertainty. As written, this section implies that the only risk is one of biosafety, when the inadvertent blocking of essential solutions is also at stake. Much environmental damage has already been done by other technologies. New developments in synthetic biology do not exist in a technological vacuum, but must be assessed in relation to the impact that existing technologies have on the world, such a climate change and loss of biodiversity from deforestation, and the potential for synthetic biology to develop solutions that can help reverse this damage and generate a more sustainable world for generations to come.	Comment noted.
Western Michigan University	12	49	This statement reverts to the first view of synthetic biology as a single discipline. Clarity is needed in this regard. It is not simply a matter of semantics; it indicates a perspective on the way regulations are developed	Revision made.
IWF	12	49	The reasons for the term single discipline should be elaborated	Revision made
Global Industry Coalition	12	49	**Delete** "*new*" Synthetic biology is referred to as new discipline. Not only is this inconsistent with the broad definition the authors have applied, it fails to recognise that it builds on long-existing disciplines and is part of a continuum of biotechnological developments.	Revision made.

Global Industry Coalition	12	50	**Replace** text. These are broad statements that need to be justified with evidence. It would be more balanced and factual to replace line 50 and state that "*...and it is possible that existing regulatory mechanisms may need adaptation on a case-by-case basis to comprehensively assess new types of environmental applications, for example the information required for a risk assessment of an LMO containing an engineered gene drive*."	Comment noted.
Expert committees of DFG	13-14	28-7	Communication, engagement and transparency => These chapters should removed or reformulated after clearly defining the term of SynBio. [RS] I've clarified this and also that the key messages addressing these issues are not dependent on a definition of synbio.	See scope and methods for more clarity on definition and scope.
Imperial College London	13	01	Again here it is stated "the potential impacts of synthetic biology" is referring to one single discipline. However, since it involves such a wide technical area is, it is more likely that different synthetic biology technologies may have very different impacts.	Revision made.
WHO	13	01-07	Reference could perhaps be made to BWC and CWC General Purpose Criterion (GPC).	Revision made.
Federation of German Scientists & ENSSER	13	03-07	How about products?	Editorial suggestions noted and revisions made.
Global Industry Coalition	13	04	**Insert** "*LMO*" prior to "*biosafety*" and **delete** "*conventional LMOs*". LMOs are LMOs, "conventional LMO" is meaningless.	Editorial suggestions noted and revisions made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	13	04	The term "conventional LMOs" is not widely used and its meaning remains unclear in this context. Please consider using the term "transgenic LMOs" or "classical genetic engineering" (c.f. p. 131 l. 43).	Revision made
Federation of German Scientists & ENSSER	13	04	RREPLACE: ~~conventional~~ **first generation** LMO ("conventional LMO" is a misnomer)	Revision made

Global Industry Coalition	13	05	**Delete** "*already include some of these complex elements*" and replace with "*accommodate the potential expansion of types of LMOs and applications.*".	Editorial suggestions noted and revisions made.
JCVI	13	05-07	The statement in point 14: 'Adapting existing frameworks in order to "future proof" them for synthetic biology', in my view, is a more justifiable and accurate statement than that a "new paradigm" is needed, as stated in point 12.	Revision made.
Global Industry Coalition	13	06	**Insert** "*where necessary*" after "*frameworks*".	Editorial suggestions noted and revisions made.
Federation of German Scientists & ENSSER	13	06	"concerted effort from all stakeholders". The processes available are not balanced and there are vast power discrepancies as well as resource discrepancies. Unless these are properly balanced any efforts will be largely in vain to achieve an agreeable outcome.	Revision made.
UK EBLC	13	09-28	I agree that there are significant differences in these laws between jurisdictions and it is worth considering whether there should be a more streamlined and uniformed approach to regulation. This would make it easier and more transparent for technological development and also easier for less developed nations to bring their regulatory frameworks up to date. This would have the benefit of widespread consistency and prevent unethical developments in less well regulated jurisdictions.	Comment noted.
Global Industry Coalition	13	09-28	**Revise** Paragraph 15 for factualness. As it is written, it is misleading - the authors are implying that all synthetic biology uses need to be covered under a single regulatory regime. No products have such regulatory coverage, and this cannot be the case for synthetic biology either (and especially where there is no clear definition of it). This needs to focus clearly on the CBD rather than promote expansion of the CBD regulatory scope (and in the absence of understanding on what is "appropriate" regulations).	Comment noted.
Expert committees of DFG	13	14-25	For example, the replacement of natural products with products resulting from synthetic biology could 14 lessen the pressure on natural habitats but	Comment noted. Key messages section has been restructured.

			could also disrupt in situ conservation projects. There may be 15 the need to consider creating rules for specimens produced from synthetic or cultured DNA as the 16 demand for them could not only lead to an increase in the demand for (illegal) natural specimens, but 17 they could also be mixed with (illegal) natural specimens. The displacement of some of the natural 18 products (i.e. naturally occurring molecules obtained from plants) can also potentially ease negative 19 pressures on wild or cultivated species, but it can also displace cultivation practices, often in topical and 20 sub-tropical regions. If not handled sensitively, this therefore may bring them into conflict with, or 21 displace, those naturally sourced products which underpin the livelihoods and fragile economies of 22 smallholder producers. Similar situations and examples could be cited for other synthetic biology 23 applications. This complex web of potential interactions derived from the use of synthetic biology 24 applications in various scenarios is therefore adding to the challenges of assessing the potential impacts 25 that could be associated with their use. => This part should not be considered as of SynBio but instead addressed in the context of agricultural development / seed development and use. Again, product- and use-related risk assessment, not on the method of generation / construction of species/strains	
Expert committees of DFG	13	18-21	It is unfounded to expand the mandate of CBD into regulation of SynBio. Let's assume a new chemical synthetic pathway for a natural product is developed and will replace a nature-derived product that would provide income to IPLCs. CBD would not consider this. However, such product made by metabolic engineering would fall under CBD. This would base regulatory oversight on the process and not on the product, which makes little sense with respect to the outcome. Example: Vanillin, chemically synthesized or produced from biological precursors such as wood chips, would not be considered under CBD. Vanillin produced by fermentation of engineered yeast would be considered synthetic biology under CBD. Same compound, different regulations, based on the method of production. The intrinsic multidisciplinarty and the plethora of stakeholders, together with the fast pace of scientific and social development requires many other	Comment noted.

			actors, e.g. industry, research, education, to be involved. Starting of course with the experts themselves.	
GJSG on SynBio	13	18-21	There is no need to expand the mandate of CBD into regulation of SynBio. General regulation of products from synthetic biology likely is an obstacle for the transition from fossil to renewable ressources (bio-economy) as it favours traditional chemical production of the same products. It should be noted that the traditional production of natural product-derived pharmaceuticals or fine chemicals and solvents requires ressourcing largely from plants thus exerting tremendous stress on natural ressources and ecosystems.	Comment noted.
Global Industry Coalition	13	21	We agree with the phrase "*without the need to invent/create another series of fora*"	comment noted.
Western Michigan University	13	22	See previous comments on synthetic biology as a single discipline.	Revision made.
EBRC	13	23-26	Agree with this statement. No one entity is going to be able to handle global regulation of Synthetic Biology methods, products, and deployments.	Comment noted
UK EBLC	13	29-38	This is basically a reframing of point 15.	Revision made
WHO	13	Key message 16	Perhaps also include "best practices and shared principles"	Revision made.
Western Michigan University	13	31	Refer to Entine J, Felipe MSS, Groenewald J-H, et al (2021) Regulatory approaches for genome edited agricultural plants in select countries and jurisdictions around the world. Transgenic Research. https://doi.org/10.1007/s11248-021-00257-8	Editorial suggestions noted. The authors are refraining from using citations in the Executive Summary and Key Messages. Entine et al. (2021) cited in document.
Global Industry Coalition	13	31	**Delete** "*fragmented*". The landscape is not "fragmented", it is just multi-faceted.	Editorial suggestion noted

Federation of German Scientists & ENSSER	13	32	"by the large number of near market applications" please be clear about numbers. Large number does not mean anything.	Revision made
PRRI	13	32-33	This is contradictory, the text both argues on the need of a horizon scanning to identify synthetic biology that threatens the existing regulatory framework and here it states that there is a large number of near-market applications. When giving real examples of synthetic biology applications further in the text the number of applications is not large.	Comments are noted. Revision made.
Global Industry Coalition	13	33-34	**Revise** for factualness. The authors should refrain from using statements such as the following: "*there is a growing urgency to discuss the evolution of a more cohesive international regulatory environment*" in the absence of evidence in the report for such need.	Comments are noted. Revision made.
Federation of German Scientists & ENSSER	13	34/35	"Moreover, as synthetic biology will continue to grow in relevance and importance due to the opportunities that it offers towards solving global challenges..." This, as discussed in the beginning, is an unsubstantiated claim and assumption. Without proper and reliable broad spectrum multidisciplinary benefit analysis - which is at present not possible as there are no agreed methodologies nor experience nor agreed societal values or requirements and framework - and given the speculative nature of many of the claims, such a statement is not helpful in this context, nor should it be the basis for policy suggestions and further actions.	Revision made.
JCVI	**16 (13!)**	33, 34	Perhaps "coordinated" international regulatory environment is a better term than "cohesive" regulatory environment. This would be a good place to at least name the other international players discussed in the full document, e.g., WHO, FAO, WIPO, etc.	Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	13	35	"due to the opportunities" consider adding the word "potential" before opportunities, as most of those applications have not proven to be beneficial at this stage.	Editorial suggestions noted and revisions made.
ISF	13/14	Table 1	See comment above. (page 10; Lines 43-45)	See scope and methods.

Expert committees of DFG	13-14	Table 1	should be restructured, parts not addressed as SynBio. Examples: • Plant-based vaccines • Engineered phages as anti-microbials. • Engineered probiotics for the production and in vivo delivery of medicines. • Genetically engineered nitrogen-fixing bacteria and other genetically engineered bacteria for agriculture. • Genetically engineered plants to produce recombinant polyclonal antibodies against snake venom toxins. • Genome edited crop plants and farm animals. • 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 soya bean and oilseed rape. • Biological nitrogen fertiliser based on engineered bacteria. • Genetically engineered bacteria for environmental applications, such as bioremediation, biodegradation and biomining. • Conservation purposes and control of vector-borne disease. • Improving the resilience of wild animal and plant populations	see Scope & Methods
UK EBLC	13-14	Table 1	'food and food ingredients' is listed, but the significance of biodiversity is not reflected. The potential to reduce demand for meat through substitution could have profound benefits in terms of reducing pressure to deforest rainforests and other sensitive lands by diminishing both the grazing land area required and that for growing soya and other cattle feed components. 'Genome edited crop plants and farm animals' should also include the words 'to confer disease resistance and resilience to other environmental challenges' By simply listing issues without noting the potential benefits from the application of synthetic biology in these areas, there is a risk that these topics may be simply reviewed as a risk or as an unnecessary technological intervention, instead of a positively-motivated innovation in response to marketplace needs and challenges.	Comment noted.

Imperial College London	13	40	In Table 1 Engineered gene drives in mosquitoes for control of vectorborne diseases and Engineered gene drive for an agricultural pest are listed in the advanced stage. All of these gene drives are still under research and development. There have been no field trials and all results so far are based on experiments done in laboratory populations. Therefore, these examples fall still under the research stage.	Revision made.
EBRC	13	40	Table 1 row 1, column 2, bullet 3 mentions recreation of 'extinct infectious horsepox' as a very specific use of synthetic biology in a research context. The remainder of the bulleted items in this row and column are all categorical applications of synthetic biology – recommendation that this bullet, too, reflect a category of usage rather than a specific, one time use, e.g. 'synthesis of viral genomes from chemically synthesized DNA fragments'.	Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	13	40	Table 1. Please consider including a definition of categories used, especially "advanced development".	Revision made.
Federation of German Scientists & ENSSER	13	40	Table - General comment I am surprised that all the listed developments are categorised as synthetic biology. Further I find the categories unclear, both for "intended use" as well as what is understood to be "advanced development" and what is "commercially available". There should be extra columns to show if an organism or product for intended containment could survive or spread into the environment, commercially available does needs to distinguish between what is actually being used and on the market or what is simply not being taken up or no longer taken up. Advanced development needs the clearest definition and from my perspective would include that field tests or equivalent product tests have been carried out, and that it is clearly beyond the actual initial research stage.	Revision made.
PRRI	13-15	Table 1	- Please add references to the examples given - Some examples given are not synthetic biology - Please consider relevance to CBD aims and scope to the examples given	Revision made.

			- Applications listed as “Unmanaged or wild settings” are likely to fit better as “semi-managed”	
Global Industry Coalition	14	-	**Revise** Table 1 for factualness. We note that the authors have used ‘inclusive’ approach to identifying applications of synthetic biology, however some of the listed applications are approved LMOs, LMOs under development, or are products that are not covered under biotechnology regulations and cannot be presented as examples of synthetic biology applications. Please remove the following from Table 1: • 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 Please substantiate with evidence that the “engineered drive for an agricultural pest” is in advanced development.	Revision made.
Federation of German Scientists & ENSSER	14	bottom	Unmanaged or wild settings: this should also include algae in the research column and gene drive mosquitoes in the Advanced development column	Revision made.
CDTBE-UK	14	Table	The report should have references for every technology mentioned in the table.	Revision made.
IWF	14	Table	Source and references should be mentioned	Revision made.
Max Planck Institute for Terrestrial Microbiology	14	Table	Some of the genome-edited plants listed would not be considered “synthetic biology” products, but rather products of classical genetic engineering. Some plants would be eventually even not considered GMOs (in case of single-base	Revision made. See scope and methods clarity on scope.

			modifications that occur also naturally). Again no clear definition of "synthetic biology"	
Expert committees of DFG	14	Table 1, 2nd row	Unclear why a range of genome-edited plants are mentioned here. They wouldn't be considered products of synthetic biology, in several cases not even as GMOs. The sole process of gene-editing a plant does not imply it will be a synthetic biology product, most of the examples given are just classical genetic engineered products. The definition of a synthetic biology product is not clearly stated throughout the text.	Revision made. See scope and methods clarity on scope.
Outreach Network for Gene Drive Research	14	Table 1	It may be premature to characterise "engineered gene drives in mosquitoes for control of vector-borne diseases" and "engineered gene drive for an agricultural pest" as in "advanced development" as both applications have not undergone field trials and are many years away from being ready for use.	Revision made.
GJSG on SynBio	14	Table, 2nd row	Genome-edited plants cannot be considered synthetic biology products, not even GMOs. The examples are classical genetically engineered products. The lack of a sound definition of a synthetic biology product is obvious.	Revision made. See scope and methods clarity on scope.
Global Industry Coalition	15	11	The statement "*While there is no internationally agreed definition of "synthetic biology*" should be captured in the Executive Summary which currently misses this nuanced but important information.	Editorial suggestion noted and revision made.
Global Industry Coalition	15	13	**Delete** "*is*" and replace with *"they proposed, of:"*	Editorial suggestion noted.
Global Industry Coalition	15	19	**Insert** "*tools,"* prior to "*techniques*" and **insert** "*and applications*" after "*techniques*".	Editorial suggestion noted and revision made.
ISF	15	22	The authors refer to applying the broadest interpretation of synthetic biology which leads to inclusion of each and any method of biotechnology as synthetic biology in their report. In this regard we question whether the title of document is correctly reflecting its contents or should rather be "Biotechnology" to more correctly represent the general approach taken by the authors.	See scope and methods.

Global Industry Coalition	15	22	If the broadest interpretation is maintained, the authors are not describing synthetic biology but "modern biotechnology" and "biotechnology" more generally. If the authors do not reduce the scope of applications captured in their report, there should be a consideration whether the report is providing an update on synthetic biology or biotechnology.	see scope and methods.
UK EBLC	15	24	This and other statements throughout the report, whilst admirably attempting to deliver a balance of views received during the consultation phase, fail to offer a similarly balanced assessment – mixing private opinions and conjecture with peer-reviewed scientific content. For this document to have credibility it is important to note that lack of peer review impacts the credibility and impartiality of the information, and failure to weight such statements appropriately risks delivering a skewed impression to the non-expert reader.	See scope & methods.
Max Planck Institute for Terrestrial Microbiology	15	13 ff	Use of "synthetic biology" as very inaccurate "blanket definition" for classical biotechnological efforts.	See scope and methods/
Expert committees of DFG	15	13-16	Definition used here does not allow for a distinction between canonical biotechnology and synthetic biology. It rather leads to a "catch-all" that puts any genetic engineering under the SynBio umbrella.	See scope and methods.
GJSG on SynBio	15	13-16	Biotechnology based on traditional genetic engineering is not synthetic biology. The latter rather is a suite of very efficient and precise tools allowing for precisely constructing biosynthetic pathways.	Revision made.
Western Michigan University	15	32-33	Here, the document seems to take a skeptical view of the term "synthetic biology" because of the lack of a clearly established agreement on what that term encompasses. Therefore, it cannot be a single discipline.	Revision made.
Western Michigan University	16	23	Commercialisation has to be defined, since some important applications of synthetic biology will not be distributed through a commercial enterprise.	Revision made.

IWF	16	23	It should be noted that the use of synthetic biology can also be for non-profit.	Revision made.
Federation of German Scientists & ENSSER	16	25	DELETE: Potential impacts ~~of~~ on the	Revision made.
UK EBLC	16	44	This is an oversimplification; whilst it is true that some of the tools used in synthetic biology are also used in genetic engineering, synthetic biology represents a much wider spectrum of tools and approaches - this is exemplified, for example, in the Royal Academy of Engineering report, cited P 17 L1.	Revision made.
Federation of German Scientists & ENSSER	16	11-13	Feels that is too limited. How about interventions made?	See scope and methods.
EBRC	16	25-27	Agree with this statement. Potential impacts of Synthetic Biology on the conservation and sustainable use of biological diversity cannot be generalized. Recommend applications to be considered on a case-by-case basis.	Comment noted.
Federation of German Scientists & ENSSER	16	26-27	Re case by case: This notion as presented here is counter to discussions and deliberations over the year on the issue, and is also counter the understanding of providing guidance regarding specific blocks/or categories of LMOs, for example. A case by case is for the final stage of individual applications to the regulator but initially it is too narrow and will not provide any possibility for guidance or understanding which expertise might be required. It is desirable to categorise blocks of 'applications' (in the widest sense) and to undertake initial assessments and sufficiency of methodology, guidance and understanding. COMMENT: here - as mentioned previously - is an example of confusion of terms. For regulators (especially in the EU) and "application" is the submission of a dossier to the authorities in request of gaining approval.	Revision made.
Expert committees of DFG	16	26-28	Most of the examples chosen are not synthetic biology approaches but just canonical biotechnology/genetic engineering (Sections C and D).	See scope and methods.

GJSG on SynBio	16	26-28	Almost all examples are from classical genetic engineering (Sections C and D).	See scope and methods.
UK EBLC	16	42-44	The document is completely missing all the modelling-based design aspects of SynBio in section C 1 and 2.	Revision made.
Federation of German Scientists & ENSSER	16	43 & 44	“supporting” Technologies - see Comment page 10 line 10	comment noted
WHO	16		Perhaps further text on GMO regulatory frameworks could be incorporated	Comment noted.
Federation of German Scientists & ENSSER	17	03	Testing of “biological” systems. Which systems? Limited systems? Specific systems?	Not specific biological system, but any network of biological entities.
Federation of German Scientists & ENSSER	17	03	Reference wrong or interpretation wrong. E&W do not cover 'in silico testing of biological systems' - but rather point to the limitations of in silico predictions. Please clarify what is meant here by biological systems (which ones? how complex?) and how "testing" is being performed and for what? otherwise say "and to a limited extend in silico predictions". (this would go along with E&W, 2013).	Revision made
Federation of German Scientists & ENSSER	17	06	“longer lengths of DNA” - its not longer lengths as such, but just that more DNA can be covered/sequenced in shorter time	Revision made.
Federation of German Scientists & ENSSER	17	06	Consider replacing ‘often’ with ‘commonly’, as that is what is mostly done with current next generation sequencing.	Revision made.
Federation of German Scientists & ENSSER	17	07	COMMENT: It is however increasingly understood and reported on in recent publications that there are shortcomings to high throughput whole genome sequencing and checking against reference libraries: it is vulnerable to failing to see/identify larger chromosomal alterations, such as translocations, duplications, inversions and even some scrambling.	Revision made.

Federation of German Scientists & ENSSER	17	08	Please correct 2017 to 2016 and adjust text. According to my understanding of Shapira: The search was for the time between 2000 & 2015, the authors identified 8064 papers, though perhaps not all were counted in the final outcome (please check yourselves) - and the publications importantly also cover patents applications.	Revision made.
Expert committees of DFG	17	09	As in page 10, line 26. The origin of synthetic biology is not 1980 but 2000.	Revision made.
GJSG on SynBio	17	09	Synthetic biology emerged later, around 2000 when reports on the de novo construction of genetic circuits were published.	Revision made.
Federation of German Scientists & ENSSER	17	09	"since 1980, ..." COMMENT: is that between 1980 and 2019? and how come between 1980 & 2000, where Synbio really wasn't a topic or an approach. Please clarify.	Revision made.
Global Industry Coalition	17	09	**Insert** "*body of research identifying itself as*" prior to "*synthetic*" and **delete** "*research*" from this sentence.	Revision made.
Global Industry Coalition	17	18	**Replace** "*raising*" with "*increasing*".	Editorial suggestions noted and revisions made.
Imperial College London	17	21	The focus is very much on commercial value, however some of those technologies are also developed to improve public health and conservation, which will not be distributed commercially.	Revision made.
Global Industry Coalition	17	22	**Replace** "*could*" with "*are".*	Editorial suggestions noted and revisions made.
CDTBE-UK	17	25	Remove 'chemical' from title because enzymatic synthesis also has potential.	Editorial suggestions noted and revisions made.
PRRI	17	25	Delete the word "chemical" as reliance on chemical synthesis may change as other methods are being developed.	Editorial suggestions noted and revisions made.

EBRC	17	25	Given the inclusion of enzymatic synthesis in this summary, recommendation to change the title of the section to 'Synthesis of DNA' or 'Ex Vivo Synthesis of DNA'.	Editorial suggestions noted and revisions made.
Global Industry Coalition	17	32	**Revise** for factualness. "*genome-length DNA strands*" is misleading given that genomes are of different sizes, and the cited article does not provide such examples.	Revision made.
Expert committees of DFG	17	01-03	This actually leads to safer products	Comment noted.
GJSG on SynBio	17	01-03	This actually leads to safer products	Comment noted.
UK EBLC	17	08-09	this statement seems somewhat out of date: *By 2017, more than 25,000 authors at 3700 organisations located in 79 countries had contributed to the 8 synthetic biology research (Shapira et al., 2017).*	Comment noted.
Global Industry Coalition	17	15-16	In this sentence it is not clear here how many funding bodies for Germany, Japan, UK, EU	Revision made.
Federation of German Scientists & ENSSER	17	22-23	Agreed, but also there seem to be divergent views on why calling it "supporting" technologies (please see comments for page 10 line 10)	Comment noted.
Global Industry Coalition	17	23-24	**Delete** "*some of the more widely used tools*" and replace with "*biotechnology technologies and tools that have emerged since the 1990s* , ... " This is a more accurate description of the following sections, which in essence present information about developments in biotechnology that are not "classic" rDNA approaches, and labels them as synthetic biology.	Revision made.
EBRC	17	29-30	Recommendation that this sentence be removed or be rewritten to emphasize the universality of the limitation on per-oligo synthesis length. No chemical or enzymatic device, at present, can create gene-length strands of DNA without an assembly step. It is unclear if this sentence is referring to devices that combine synthesis with assembly protocols but lines 42-46 on this same	Revision made.

			page accurately describe the state of the art (in that chemical and enzymatic synthesis is limited to oligo-length fragments which must then be assembled).	
Global Industry Coalition	17	29-30	**Delete** "*Using proprietary techniques, machines can also create DNA strands up to the size of a gene, hundreds, or thousands of base pairs in length.*" The sentence correctness is questionable and should be deleted unless clearly supported by evidence that "thousands of base pairs" can be synthesized (rather than assembled).	Revision made.
UK EBLC	17	34-36	Whilst this statement is true, it represents one of the key foundations of synthetic biology – i.e. to produce DNA chemically, accurately and at low cost. Also, it should be stressed that DNA synthesis is a commercial field that is developing rapidly with new techniques and new companies.	Revision made.
WHO	17		Actual price offers for custom oligo sequence synthesis could perhaps be included	General comment noted
ISF	18/19	20-25	Whole chapter 1.3 on "genome editing". As stated previously we oppose equalling any application of genome editing with synthetic biology. Please revise section 1.3 to better reflect that methods of genome editing are merely an enabling technology and by themselves are not synthetic biology. This applies particularly to examples where simple mutations are introduced. Why do you consider SDN1 applications synthetic biology and how would this be a "new dimension of modern biotechnology"?	Revision made
PRRI	18-19	19 - 1.3. Genome editing	Genome editing tools and techniques can be used in many different ways. They are not reserved to be used exclusively in synthetic biology. It needs to clarify when included and excluded to synthetic biology.	Revision made
Global Industry Coalition	18	05	**Revise** for factualness. Why is it stated that directed evolution is a "*biotechnology method often employed for synthetic biology*" ?	Revision made.
Global Industry Coalition	18	05	**Insert** "*some of which are*" before "*based*".	Revision made.

Western Michigan University	18	09	Random mutagenesis is a traditional tool. Selection of random mutants would be out of scope of the Cartagena Protocol, but as mentioned in 8.1.4(a) is in the scope of the CBD.	General comment
CDTBE-UK	18	11	This misses the fact that directed evolution could help the development of new or more efficient enzymes, allowing medicine to gain access to new chemical reactions or perhaps new compounds with beneficial properties. The targeted evolution of enzymes in fields like drug discovery could boost the arrival of personalised medicine to the clinics (https://doi.org/10.1042/ETLS20200047).	Revision made.
Global Youth Biodiversity Network-Uganda	18	13	A technology called multiplex automated genome engineering, developed by ..???? (Wang et al ., 2009)	Revision made.
Global Industry Coalition	18	25	**Replace** "*mammal*" with "*mammalian".*	Editorial suggestions noted and revisions made.
Federation of German Scientists & ENSSER	18	30	Please ADD & ALTER, as otherwise a wrong or misleading impression is given "These approaches do **mostly but** not ~~necessarily~~ **always** require the stable..."	Editorial suggestions noted and revisions made.
CDTBE-UK	18	32	"Supposed" to be degraded by the cellular metabolism - these oligos have no real long-term permanence and will be degraded. This language makes it feel like there is opportunity for these oligos to survive and cause later damage on non-intended targets; this is almost certainly not the case, as these oligos are fragile and readily degrade without the need for active metabolism.	Revision made.
Global Industry Coalition	18	32	**Delete** "*supposed to be*" and **replace** with "*subsequently*".	Revision made.
Federation of German Scientists & ENSSER	18	33	ADD: "..**eventually** degraded by ...."	Revision made.
Federation of German Scientists & ENSSER	18	34	ADD: "..transgene **(which is commonly done for plants, as well as in many animal settings)** or introduced..."	General comment noted

Federation of German Scientists & ENSSER	18	37	Just a grammatical correction: "... final host organism ~~and~~ are heritable.."	Revision made.
CDTBE-UK	18	41	"Better oil quality" - could emphasise that this addresses reducing the need for partial hydrogenation of soybean (Trans-fats), which is a significant contributor to heart disease. See also paper on TALENs for increasing crop shelf life/lowering acrylamide levels in potato (https://doi.org/10.1111/pbi.12370)	Revision made.
Federation of German Scientists & ENSSER	18	41	"improved" is a specific point of view, which may be different from a biodiversity point of view or agroperformance or food-web poin of view. Please ALTER: " ...bean with ~~improved~~ **altered** oil quality **or composition** ...."	Comment noted.
Third World Network	18	42	The statement "TALENs are recognised for their high degree of precision and control" lacks consensus and is challenged by evidence of unintended effects. An illustrative example is the hornless cattle recently developed in the US, that was later found to have accidental integrations of plasmid DNA, including antibiotic resistance genes (Norris et al., 2020). It is vital that introductory text to technologies is accurate, and not based on unsubstantiated claims of utility or efficacy. Norris, A. L., Lee, S. S., Greenlees, K. J., Tadesse, D. A., Miller, M. F., & Lombardi, H. A. (2020). Template plasmid integration in germline genome-edited cattle. Nature Biotechnology, 38(2), 163–164. https://doi.org/10.1038/s41587-019-0394-6	Revision made.
ETC Group	18	42	Says TALENS have a high degree of precision and control, but there is strong evidence from hornless cattle recently developed in the US, that this is not the case. They were later found to have accidental integrations of plasmid DNA, including antibiotic resistance genes (Norris et al., 2020 - https://www.technologyreview.com/2019/08/29/65364/recombinetics-gene-edited-hornless-cattle-major-dna-screwup/). It is vital that introductory text to technologies is accurate, and not based on unsubstantiated claims of utility or efficacy. Norris, A. L., Lee, S. S., Greenlees, K. J., Tadesse, D. A., Miller, M. F., &	Revision made.

			Lombardi, H. A. (2020). Template plasmid integration in germline genome-edited cattle. Nature Biotechnology, 38(2), 163–164. https://doi.org/10.1038/s41587-019-0394-6	
African Centre for Biodiversity	18	42	It is vital that introductory text to technologies is accurate, and not based on unsubstantiated claims of utility or efficacy. Here it says that TALENS have a high degree of precision and control, but there is strong evidence that this is not the case, including accidental integrations of plasmid DNA including anti-biotic genes. Norris, A. L., Lee, S. S., Greenlees, K. J., Tadesse, D. A., Miller, M. F., & Lombardi, H. A. (2020). Template plasmid integration in germline genome-edited cattle. Nature Biotechnology, 38(2), 163–164. https://doi.org/10.1038/s41587-019-0394-6 Norris et al., 2020 - https://www.technologyreview.com/2019/08/29/65364/recombinetics-gene-edited-hornless-cattle-major-dna-screwup/	Revision made.
Federation of German Scientists & ENSSER	18	46	ADD: "..... almost all **genome editing** studies and ...."	Editorial suggestions noted and revisions made.
Third World Network	18	47	It is not clear that base editing is indeed being used for almost all studies of market oriented traits. This does not align with current publications on editing technologies and if indeed is true, it should be substantiated with references.	Comment noted.
Third World Network	18	47	It would more accurate to state that CRISPR-Cas systems have led to '*preliminary research advances*' rather than advances, which implies commercialised advances have been made in the fields of plant and animal engineering and health applications. The overwhelming majority of CRISPR use is still at the preliminary research stage without demonstrable 'advances' for commercialised products.	Editorial suggestions noted and revisions made.
ETC Group	18	47	Using the term "advances", implies that applications have been made in the area of plant and animal engineering and health applications. The	Editorial suggestions noted and revisions made.

			overwhelming majority of CRISPR use is still at the preliminary research stage without demonstrable 'advances' for commercialised products. It would therefore be more accurate to state that CRISPR-Cas systems have led to 'preliminary research advances' rather than.	
Federation of German Scientists & ENSSER	18	47	ALTERATION: " ~~..... have been addressed by genome editing~~." Replace with to enhance clarity: "**are being investigated or addressed by genome editing research**."	Editorial suggestions noted and revisions made.
Federation of German Scientists & ENSSER	18	48	"applications". What please is meant by 'applications' here? Do you mean its use in laboratory research? General application of a technology? Submissions to regulators for approval or field testing? please explain/define, as 'application' can be understood to be a final product that is being tested for marketing, or it can be a certain category, such as herbicide tolerance.	Revision made.
Federation of German Scientists & ENSSER	18	48	Please ADD at the end to add clarity and better understanding ".... has increased exponentially worldwide, **often in aid to understand gene functions and related traits, as well as to improve the methodologies and increase efficiency and reduce off-target effects (for plants see Eckerstorfer et al. 2019)**.	Editorial suggestions noted revision made
African Centre for Biodiversity	18	49	The overwhelming majority of CRISPR use is still at the preliminary research stage without demonstrable 'advances' for commercialised products. It would therefore be more accurate to state that CRISPR-Cas systems have led to 'preliminary research advances' rather than "advances"	Editorial suggestions noted and revisions made.
Federation of German Scientists & ENSSER	18	49	ALTER: "..... ~~and~~ **. This** has led to advances in plant and animal **genetic studies and** engineering and ..... "	Editorial suggestions noted and revisions made.
UK EBLC	18	05-18	The section as presented here is not correct from a scientific perspective. The term directed evolution is used in the context of evolving the specificity and/or function of individual proteins. It has been on-going since the early 90s and usually uses in vitro techniques like error-prone PCR to introduce mutations to a single gene. In vivo gene directed evolution where a specific	General comment noted. Revision made.

			gene is targeted for evolution inside the cell is a more recent development, best exemplified by the PACE system. Genome directed evolution is an even more niche activity with the use of techniques like MAGE. While CRISPR has been attempted for use in this regard it is limited in its capability and is not widely used.	
EBRC	18	02-03	This sentence should clarify whether the benchtop devices described refer to any benchtop device (low-throughput phosphoramidite synthesis machines have been available on the benchtop for many years) or specifically to enzymatic devices capable of gene-length synthesis. The timeline appears to refer to the latter.	Editorial suggestions noted and revisions made.
Global Industry Coalition	18	04-25	**Major revision needed**. The section on genome editing is technically detailed and it lacks context. It is very unclear why this section is not focusing on how genome editing is used in **synthetic biology**. Why are the outcomes described (e.g. SDN-1 types changes) considered relevant to synthetic biology? Some of these changes might be one or very few base pairs, how is this a "*new dimension of modern biotechnology*"? Even SDN-3, which results in outcomes comparable to so-called "classical" transgenics, cannot be described as a "new dimension".	comment noted
JCVI	18	02, 03	Clarify that benchtop DNA “assemblers” have been available for several years (Codex DNA) but enzymatic “printers” are expected in the next year or two.	Comment noted and revisions made
Federation of German Scientists & ENSSER	18	27-29	ADD or REPLACE: “....(TALEN), and CRISPR-Cas9 (or alike). These techniques site directed nucleases can be engineered to bind to DNA sequences 27 in specific manners (Carroll, 2013; Gaj et al., 2016; Lienert et al., 2014). Approaches using SDNs and ODM 28 are applied to introduce random (SDN-1) or directed specific or pre-designed sequence ...”	Editorial suggestions noted and revisions made.
Expert committees of DFG	18	30-35	In many cases there is no need for stable transformations, this is becoming common practice. Again editing (which per se is not necessarily synthetic biology, exceptions articles of Zsögön et al 2018 & Kwon et al 2020) is	General comment noted

			confused with gene drive throughout. There must be a clear distinction between methods and procedures and a synthetic biology approach (that might use those techniques). It is confused throughout the entire document.	
Global Youth Biodiversity Network-Uganda	18	36-37	The respective changes and transgenic insertions present in the final host organism are heritable	Revision made.
African Centre for Biodiversity	18	46-47	The current suggestion that base editing is being used for almost all studies of market-oriented traits does not align with current evidence and publications on editing technologies. If this is the case this must be substantiated with references.	Comment noted and revisions made
WHO	18	Line 13	"developed by (Wang et al., 2009)" – this phrasing seems incomplete.	Editorial suggestions noted and revisions made.
Global Industry Coalition	19	4	**Replace** "*having impacts in agriculture, especially in*" with "*being applied with the aims of*" This will ensure the language is neutral and factual.	Editorial suggestions noted and revisions made.
Global Industry Coalition	19	6	Combining agricultural traits is also possible with conventional breeding techniques, it is just more efficient with genome editing.	Editorial suggestions noted and revisions made.
Federation of German Scientists & ENSSER	19	06	"... it is now possible to ..." This sentence is said much to general, whilst in fact these are first attempts in a direction that is not yet clear if it works the way some hope it might. Thus caution and restrain in the message is required.	Revision made.
Federation of German Scientists & ENSSER	19	16	"and may soon appear commercially" - All of these will still require risk assessment, and experience shows that obtaining a specific trait does not necessarily make it an agronomic successful plant or a biodiversity friendly plant.	comment noted

Global Industry Coalition	19	18	Targeted point mutations are not synthetic biology. Point mutations are possible with other techniques that are not biotech. This is not a "new dimension".	comment noted
Third World Network	19	19	Describing base editing as 'precise' is scientifically premature. Studies have reported unintended effects including off-target activity that challenge assertion of 'precision'. E. Zuo et al. Cytosine base editor generates substantial off-target single nucleotide variants in mouse embryos. Science. Published online February 28, 2019. doi:10.1126/science.aav9973. http://science.sciencemag.org/content/early/2019/02/27/science.aav9973	Suggestion noted.
African Centre for Biodiversity	19	19	As stated above, describing base editing as 'precise' is scientifically premature. Studies have reported unintended effects including off-target activity that challenge assertion of 'precision'.	Suggestion noted.
EBRC	19	29	Rather than being a genetic element, Wolbachia is a bacterium that, in some genetic contexts, impacts reproductive success of the host and can skew ratios of males and females. There is not a consensus that Wolbachia should be classified as a Gene Drive.	Revision made.
Federation of German Scientists & ENSSER	19	29	Again, Wolbachia should not be viewed or treated as a natural "gene drive system", as it attempts to blurr the boundaries, which is unhelpful for scientific debate, clarity, risk assessment and risk perception. If this document wants to elaborate and look at the different sides of arguments and debate, then this should be done carefully. Yet to portray matters from one specific point of view only, namely the view of gene drive developers, then this is not suitable for this CBD update report.	Editorial suggestions noted and revisions made.
Western Michigan University	19	38	An increase in gene frequency can be the result of other mechanisms, not just a result of gene drive. For example, natural selection also increases the frequency of an allele. That point should be made here.	Revision made.

IWF	19	38	There are also other factors responsible for gene frequency which should be mention.	Comment noted. Revision made
Outreach Network for Gene Drive Research	19	38	Phenomena other than gene drives can also cause increases in the frequency of inheritance of a particular genetic element in a population (e.g. natural selection).	Comment noted. Revision made
Imperial College London	19	38	Natural selection also favours inheritance of certain traits	Comment noted. Revision made.
Global Industry Coalition	19	38	It should be noted that frequency of gene inheritance can be the result of other mechanisms such as natural selection	Comment noted. Revision made.
Global Industry Coalition	19	41	**Delete** "*can*" and **replace with** "*may*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	19	41	**Insert** "*Laboratory-based testing indicates that*" before "*These CRISPR*".	Editorial suggestions noted and revisions made.
Imperial College London	19	43	It should be stated that the gene drive will produce offspring that "potentially" all carry the gene drive, as often the homing rate is not 100% due to non-homologous end-joining (NHEJ).	Editorial suggestions noted and revisions made.
Federation of German Scientists & ENSSER	19	02-03	I neither understand this sentence nor does it seem to be fitting at this place.	comment noted
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	19	04-05	"CRISPR-Cas technology is having impacts in agriculture, especially in increasing plant yield, quality, disease resistance and herbicide resistance, breeding and accelerated domestication (Zhu et al., 2020)." The technology can only have impacts on agriculture if products on the market have been shown to have a measurable impact. This is currently not the case for the mentioned applications. Please rephrase by e.g. "is expected to have".	Editorial suggestions noted and revisions made.
Federation of German Scientists & ENSSER	19	04-05	"CRISPR-Cas technology is having impacts in agriculture, especially in increasing plant yield, quality, disease resistance and herbicide resistance, breeding and accelerated domestication (Zhu et al., 2020)."	Editorial suggestions noted and revisions made.

			As stated above, this is a wish-list but not a reality. ODM herbicide tolerance has been achieved, the benefits though of which are being argued with regards to impacts on biodiversity due to herbicide applications. It is indeed one of the easiest traits and most popular traits to genetically modify/engineer and to bring to market.	
Third World Network	19	04-08	Repeated point to that above (pg 8 line 14). The examples listed here are not evidence of agricultural advances, but preliminary research without demonstrable advances to agriculture. The Zhu et al., (2020) review referenced for this statement summarises CRISPR studies that are again, overwhelmingly in the preliminary research stages, including investigational crops assessing candidate gene targets, few of which adequately, if at all, have conducted field trials that demonstrate traits such as increased yield. A number of studies referenced by Zhu also display unintended effects that may impede commercialisation, and cannot yet thus be considered marketable or advancing agricultural impacts. One of numerous examples, is the tomato engineered for increased 'quality' to produce elevated levels of lycopene, which concomitantly adversely affected fruit maturation (Li et al., (2018). Lycopene Is Enriched in Tomato Fruit by CRISPR/Cas9-Mediated Multiplex Genome Editing). On a broader level, 'efficacy' requires assessing the wider rationale of addressing issues of malnutrition or hunger with reductionist GE approaches, with organic tomatoes having been shown to be richer in lycopene. This example applies to other studies referenced by Zhu and should thus be carefully analysed prior to asserting that concrete advances have been made with genome editing.	Editorial suggestions noted and revisions made.
African Centre for Biodiversity	19	04-08	The examples listed here are not evidence of agricultural advances, but preliminary research without demonstrable advances to agriculture. The Zhu et al., (2020) review referenced for this statement summarises CRISPR studies that are again, overwhelmingly in the preliminary research stages, including investigational crops assessing candidate gene targets, few of which adequately, if at all, have conducted field trials that demonstrate traits such as increased yield. A number of studies referenced by Zhu also display unintended effects that may impede commercialisation, and cannot yet thus	Editorial suggestions noted and revisions made.

			be considered marketable or advancing agricultural impacts, such as Li et al., 2018, whereby the tomato engineered to produce elevated levels of lycopene, which adversely affected fruit maturation (Li et al., 2018). Therefore examples used must be carefully analysed prior to asserting that concrete advances have been made with genome editing.	
Federation of German Scientists & ENSSER	19	04-09	General comment This section is portrayed too positive and optimistic as if all of this is doable, and is just around the corner. Yet for example de novo domestication of plants has a spectrum of serious risks (including for food safety), as well as hurdles, which is being discussed in discussions elsewhere and should perhaps also have been included here. Adding to the hype will neither help the debate, nor finding solutions to achieve resilient and biodiversity supportive farming systems.	Editorial suggestions noted and revisions made.
Third World Network	19	09-10	Claims of 'precise' control of plant chromosomal recombination are highly premature and in contradiction with evidence to date on the unintended genetic effects of genome editing (see below for references on unintended effects of genome editing).	Editorial suggestions noted and revisions made.
African Centre for Biodiversity	19	09-10	Claims of "precise" control of plants chromosomal recombination are incredibly premature and in contradiction with current evidence on the unintended genetic effects of genome editing including: E. Zuo et al. Cytosine base editor generates substantial off-target single nucleotide variants in mouse embryos. Science. Published online February 28, 2019. doi:10.1126/science.aav9973. http://science.sciencemag.org/content/early/2019/02/27/science.aav9973	Editorial suggestions noted and revisions made.
Federation of German Scientists & ENSSER	19	09-10	Please ALTER to give the full picture: "CRISPR tools can **- amongst other methodologies and techniques -** also facilitate ~~the precise control of plant chromosomal recombination~~ facilitate 'controlled recombination' by inducing chromosomal cross-overs where they commonly do not occur (Taagen et al., 2020). ~~thereby~~ "**Whilst this is seen by some as** unlocking otherwise inaccessible genetic diversity**, it is seen by others as overriding the plants protective mechanisms, for example by knocking out the suppression**	Comment noted.

			genes for cross-overs. The unintended consequences of this are not known, as the whole system is still too little understood, and control is difficult."	
Federation of German Scientists & ENSSER	19	14-15	- the failure to go through to the market may in part be due to unintended effects due to the knockout of genes which may lead to the intended trait but also to other consequences, e.g. due to pleiotropic effects and altered gene regulation and feedback loops.	Comment noted
Western Michigan University	19	27-28	It is improper to refer to the patterns of inheritance observed by Mendel as laws. They are one pattern of inheritance that has been observed, but in fact there are other patterns of inheritance that occur in nature, and referring to these as aberrant is a value judgment that cannot be imposed. That perspective leads to the inference that these non-Mendelian patterns are more risky. That inference has yet to find scientific support and therefore has to be avoided when considering gene drives. See these references that describe the prevalence of non-Mendelian inheritance patterns in nature. Hurst, L. D., 2019 A century of bias in genetics and evolution. Heredity 123: 33-43.10.1038/s41437-019-0194-2 Fishman, L., and M. McIntosh, 2019 Standard deviations: The biological bases of transmission ratio distortion. Annual Review of Genetics 53: 347-372.10.1146/annurev-genet-112618-043905 Seymour, D. K. C., E.; Arioz, B. I.; Koenig, D.; Weigel, D., 2019 Transmission ratio distortion is frequent in Arabidopsis thaliana controlled crosses. Heredity 122: 294-304.10.1038/s41437-018-0107-9 Zollner, S. W., X. Q.; Hanchard, N. A.; Herbert, M. A.; Ober, C.; Pritchard, J. K., 2004 Evidence for extensive transmission distortion in the human genome. American Journal of Human Genetics 74: 62-72.10.1086/381131	Comment noted. Revision made.
Imperial College London	19	27-28	Gene Drive is not a phenomenon and that is not how it is worded in the reference that is cited. As stated in the next sentence, there are many natural gene drive systems which can favour their own inheritance.	Revision made.

ZKBS	19	27-28	The sentence “A gene drive is a phenomenon in which selfish genetic elements circumvent Mendel’s laws of independent assortment and favour their own inheritance” is phrased too colloquially. It should be rephrased more scientifically as in line 35/36: “…engineered gene drives are genetic elements that are inherited more frequently than expected based on Mendel’s laws alone.” The ZKBS would like to point out repeatedly that “gene drives” are not per se an item of synthetic biology.	Revision made.
Global Industry Coalition	19	27-28	**Revise** for factualness. The cited article does not provide for such description of gene drive. The authors should review and update this text to avoid using "selfish" "Mendel's laws of independent assortment" , "favour their own inheritance" - all of which lack scientific rigour. Consider using the publication: Standardizing the definition of gene drive Luke S. Alphey, Andrea Crisanti, Filippo Randazzo, Omar S. Akbari (2020) PNAS , 117 (49) 30864-30867; DOI: 10.1073/pnas.2020417117	Revision made.
Federation of German Scientists & ENSSER	19	27-28	This statement or definition is problematic, as selfish genetic elements -such as transposons- should not be seen in the same light as gene drives, despite recent attempts to change the terminology and alter the perception gene drives. This is not the place to add to the controversy, in particular as SGE have often a role on the evolutionary scale, in particular with regards to speciation (Critical Scientists Switzerland et al., 2019). Please simply just define engineered gene drives, as those are clearly distinct in function and purpose from natural occurring phenomena.	Revision made.
Global Youth Biodiversity Network-Uganda	19	30-31	The potential application of these natural gene drive systems to suppress populations in insects has been studied in field trials since the 1960s.	comment noted
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	19	30-31	This sentence combines two distinct observations. First, natural gene drives have been studied and second, field trials with natural gene drive have been performed. The sentence suggests that this is a heavy field of research, when combined with the list of natural gene drives in the sentence before, with extended field trials being performed. This is not the case, only few natural	comment noted

			gene drives have been tested in the field, mostly research is attempting to observe gene drives in the wild.	
Global Industry Coalition	19	32-34	The sentence captured here also applies to "genome editing". The genome editing section should be written in a similar way to this section - instead of just describing techniques it should describe applications that are/may be relevant to synthetic biology.	comment noted
Western Michigan University	19	33-34	Good point! This should be emphasized throughout.	comment noted
Outreach Network for Gene Drive Research	19	33-34	We welcome the recognition that "gene drive" refers to a broad array of approaches and applications and is best thought about in those terms rather than as a single technology. This should be stressed throughout the document. For more information on the different types of gene drives and how to refer to them, please see: • Alphey LS, Crisanti A, Randazzo F, Akbari OS. Opinion: Standardizing the definition of gene drive. Proceedings of the National Academy of Sciences Dec 2020, 117 (49) 30864-30867; DOI: 10.1073/pnas.2020417117 https://www.pnas.org/content/117/49/30864	comment noted
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	19	42-43	The statement is a theoretical prediction, not a fixed reality (c.f. e.g. resistance development). Suggestion is to replace "will" by "is intended to"	Revision made.
Global Youth Biodiversity Network-Uganda	20	07	Rates beyond those of regular Mendelian inheritance and, if its features allow, it will rapidly spread into the target population (Rode et al., 2020)	comment noted
Global Industry Coalition	20	07	**Delete** "*rapidly*". How "rapidly" it spreads depends on the generation time of the species. Take care to be factual and not imply spread at an uncontrollable rate.	Editorial suggestions noted and revisions made.
Global Youth Biodiversity Network-Uganda	20	10	RNA interference (RNAi) is an intrinsic cellular mechanism present in almost all eukaryotic organisms and	Editorial suggestions noted and revisions made.

Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	20	10	Include “in” in “an intrinsic cellular mechanism present in almost all eukaryotic organisms“	Editorial suggestions noted and revisions made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	20	25	Please consider to specify or delete “avoid food waste.” Here, it remains unclear how avoidance of food waste could be achieved by a methodology like RNAi as such. In case “avoid food waste” refers to applications such as non-browning vegetables and fruits, it might be considered that the trait is more likely modified for its aesthetic appeal to the costumer.	Editorial suggestions noted and revisions made.
CDTBE-UK	20	30	There’s not only genome search tools to identify off-target effects but also molecular dynamic simulation tools to predict the structure of RNA sequences (hairpins, loops...etc.)	Comment noted.
CDTBE-UK	20	40	and diagnostics	Editorial suggestions noted and revisions made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	20	31-32	Currently, it cannot be generally assessed whether off-target effects in NTOs are reduced by better design based on bioinformatic methods. This is due to the fact that for the majority of relevant NTOs, especially insects, no genome data are available or precise RNA binding parameters are unknown which otherwise could be considered in such a design.	Editorial suggestions noted and revisions made.
UK EBLC	20		Synthetically engineered miRNAs can be deployed as regulators in gene circuits etc. However, this area is now very important because it essentially forms the basis of mRNA vaccines to counter COVID like viruses. It will also become increasingly important in the development of antivirals.	comment noted
PRRI	20-21	9 - RNA-based tools	While synthetic biology may deploy epigenetics they are still different fields. Likewise, RNA based tools do not exclusively belong to synthetic biology. It is unwise to make a list of tools and techniques as referred to synthetic biology because these can be used in multiple fields. In addition, as Synthetic Biology	Revision made.

			develops so will additional enabling tools and techniques become available and improved.	
WHO	21	07	"production titter" should read "production titer" or titre according to preferred spelling	Editorial suggestions noted and revisions made.
Global Industry Coalition	21	07	**Remove** the additional "*t*" from "*titter*".	Editorial suggestions noted and revisions made.
CDTBE-UK	21	26	When talking about methylation, they should add that tools such as this one to modify DNA methylation could be extremely useful to do reversible changes in the genome to cure certain diseases.	Comment noted.
UK EBLC	21	27	Artificial intelligence and machine learning. These are key, developing areas of Biofoundries, referred to in page 22. The intensive use of these techniques with automation, in the context of Biofoundries, will vastly increase reliability and reproducibility, e.g. in relation to bio manufacturing.	comment noted
UK EBLC	21	37	The document asserts that AI or machine learning may enable predictions "without a need to understand the detailed biological mechanisms". While strictly true, it must be pointed out that in other areas of rapid advance in the deployment of ML tools for very large data sets analysis, there is a new trend towards understandable and explanatory AI/Machine learning. This trend has been driven both by a need to get a grip on the reasons why (i.e. the underlying discovered patterns or mechanisms) certain machine learning models make the decisions or predictions they make but also due to concerns around "bias" and other ethical considerations. Given the potentially far reaching applications of synthetic biology, we feel that there should also be more emphasis on explanatory or transparent AI/ML for synthetic biology. This will promote better trust on the science been done but also will help distil new processes and mechanisms that might be at play in the living world which a purely black box approach to AI/ML might hide.	Comment noted and revision made.

UK EBLC	21	38	The document provides a few examples of the power of AI/ML in structural bioinformatics and protein design/engineering but it seems they are failing to grasp the enormous advance made in this area in the last 3 or 4 years. Protein engineering is perhaps the more immediately fertile area where AI/ML would alter the research and translation landscape. See for example the results of the latest CASP competition. https://predictioncenter.org/casp14/index.cgi	Comment noted. Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	21	06-15	The entire paragraph should be revised in terms of language and parts of the content. It should be kept in mind that knockdowns (KD) via RNAi are not generally preferable to knockouts (KO), but that both can be used for different purposes. With KD, a residual transcription may remain, but transcription might be fine-tuned. Stable KO, on the other hand, can in certain cases be established more quickly with the aid of genome editing methods than assumed here.	comment noted
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	21	16-26	Other methods such as haploid induction or reverse breeding may as well rely on RNAi-techniques (listed in Eckerstorfer et al. 2019). These could be considered to be amended in this context. Eckerstorfer, Michael F.; Heissenberger, Andreas; Reichenbecher, Wolfram; Steinbrecher, Ricarda A.; Waßmann, Friedrich (2019): An EU Perspective on Biosafety Considerations for Plants Developed by Genome Editing and Other New Genetic Modification Techniques (nGMs). In: Frontiers in bioengineering and biotechnology 7, S. 319. DOI: 10.3389/fbioe.2019.00031.	Revision made.
CDTBE-UK	22	16	Missing the fact that these types of facilities significantly speed up the prototyping process such that Synthetic Biology can compete with other technologies to solve large scale issues such as climate change. This speed is required to address world-wide issues on time, and synthetic biology will play a key role in this in the years to follow.	Editorial suggestions noted and revisions made.
CDTBE-UK	22	17	Has a typo “Consisting of 27 non-commercial biofoundries”	Editorial suggestions noted and revisions made.

CDTBE-UK	22	17	No mention that many areas of Biosciences do not have the standardisation capability to speed up research and innovation, whereas Synthetic Biology has that potential and could indeed be used to solve world-wide problems by, for instance, using the DBTL cycle to improve the genetic parts and characterise them in a way that they can be used accurately and in a predictable manner.	Editorial suggestions noted and revisions made.
UK EBLC	22	4-17	The development and use of automation in synthetic biology, coupled to machine learning and AI are key components of the ability to undertake far more complex bio designs (e.g. in the context of gene circuits). Biofoundries are an important manifestation of the transition from traditional biology to synthetic biology – where engineering design principles are directly applied through the use of software, this coupled to automation. This allows much more complex circuits to be developed, including the ability to incorporate feedback. The creation of the global Biofoundries Alliance is an important development and now comprises around 31 Biofoundries. The ability to undertake bio design in Biofoundries leads directly to the establishment of a global design framework based on data (i.e. the manifestation of digital biology). This, in turn, will lead directly into distributed manufacturing, e.g. the manufacturing of vaccines in different locations around the world. Because the quantities required for mRNA vaccines are significantly less than for traditional vaccines, is feasible to assume that manufacturing facilities could be deployed for such vaccines within universities and research facilities.	comment noted
Global Industry Coalition	22	27-30	**Missing reference** A reference is needed to support this sentence.	Editorial suggestions noted and revisions made.
CDTBE-UK	22	Fig 1	A higher resolution image could be included here.	Editorial suggestions noted and revisions made.
IWF	22	Fig 1	The resolution of the image can be improved	Editorial suggestions noted and revisions made.

Global Industry Coalition	23-29	0	**Revision needed**. The "*Areas of Synthetic Biology research*" section is a highly confused review of developments in biotechnology and genetic engineering. At times the authors define synthetic biology as a field and at other times as tools that are used for achieving different engineering goals. It is not clear how this patchwork of information helps the reader to understand what the areas of are research where concepts of synthetic biology are actively pursued. This section contains what is "considered" by the authors to be synthetic biology. This needs to me more factual, e.g. areas of research that have emerged that have been referred to as synthetic biology under the CBD (or by practitioners), but there is no general consensus on this list. It is demonstrated (particularly in the following section 3) that these are not brand-new areas of research but are the current state of the art in a continuum of development from discoveries made decades ago.	Revision made
UK EBLC	23	07	In the document iGEM comes under the section on bio bricks. This is unfortunate, because iGEM deserves a section on its own right. It has been highly influential in developing the field of synthetic biology. One side of the synthetic biology coin is research and development, leading to industrial translation. However, for synthetic biology to become an important industry and driver of the BioEconomy (with the concomitant effects on climate change) requires a specially trained workforce. IGEM has been and is a major inspirational driver for young people to enter the field of synthetic biology. A significant number of the iGEM alumni I are now involved their own successful synthetic biology companies (many cited later in the document). In addition, there doesn't seem to be a section of the document that refers to more formal courses (e.g. in universities – undergraduates, Masters etc) or business courses specifically designed for the development of companies within the synthetic biology area.	Comment noted.
Global Industry Coalition	23	20	**Delete** "*synthetic biology"*.	Editorial suggestions noted and revisions made.

Global Industry Coalition	23	25	**Missing reference** "*Monod's Nobel prize-winning work*" was in 1965! Add reference to the year to underline the time frame.	Editorial suggestions noted and revisions made.
Global Industry Coalition	23	29	**Missing reference** Please specify from when "*Another 40 years passed…"*	Editorial suggestions noted and revisions made.
Global Industry Coalition	23	34	**Revise** Describe what were the two discrete states of switch described in "*was a toggle switch in E. coli*", otherwise this is of little value as information.	comment noted
Global Youth Biodiversity Network-Uganda	23	41-42	metabolism has gradually begun to unravel, as over the last decades numerous regulatory RNAs have been discovered.	comment noted
Global Industry Coalition	23	Footnote 7	"*not frequently included when synthetic biology is discussed*," What does this mean? Not discussed under the CBD? There needs to be better explanation in the introductory paragraph lines 16-18 regarding what is included/excluded in this section with reasons.	Revision made.
CDTBE-UK	24	12	There is an increasing number of well characterised orthogonal components such as the marionnette system (https://doi.org/10.1038/s41589-018-0168-3).	Revision made.
CDTBE-UK	24	20	The fact that protein engineering with the help of Artificial intelligence could revolutionise Biology entirely by accessing new chemistries and functions is not clearly stated. Not many other Biosciences have the potential to tweak biological function as accurately as the tools provided by Synthetic Biology. Additionally, by directly engineering proteins we can shortcut the DNA and RNA steps in the central dogma of biology. Rubisco is mentioned but not the engineered/optimised PETases, which are enzymes capable of degrading plastic (for example: DOI: 10.1126/science.aad6359).	Revision made.
Max Planck Institute for Terrestrial Microbiology	24	37	This example is classical protein engineering, but not synthetic biology	General comment noted

Expert committees of DFG	24	37-42	These are not synthetic biology approaches but just classical protein engineering	Comment noted.
GJSG on SynBio	24	37-42	A matter of definition: Usually, protein engineering is not subsumed by synthetic biology	Comment noted.
Global Industry Coalition	24	38-39	**Delete** "*are working*" and **replace** with "*have long worked*" This is not new at all - commercial GM crops have optimised Bt protein expression.	Comment noted.
EBRC	25	07	Recommend the sentence substitute "improved" with "transformed". DeepMind protein folding paper was transformative for the field – showing improved fold prediction in some cases with more than double the accuracy of previous state-of-the-art methods. If the intent of this report is to communicate advances, this sentence should be rephrased to emphasize the pace with which protein folding prediction is improving given that it was previously considered a nearly unsolvable problem. C.f. https://www.blopig.com/blog/2020/12/casp14-what-google-deepminds-alphafold-2-really-achieved-and-what-it-means-for-protein-folding-biology-and-bioinformatics/	Editorial suggestions noted and revisions made.
Global Industry Coalition	25	14	**Revise** for factualness. The use of the phrase "*with classic genetic engineering techniques.*" suggests that the tools of genetic engineering remain static while synthetic biology advances and uses a substantially different set of tools which is not the case. Synthetic biology is based on "classic" genetic engineering, it is just an extension of it. In reality, synthetic biology (as broadly described by the authors in this tech review) is the state of the art of genetic engineering and biotechnology of today.	comment noted
Global Industry Coalition	25	14	**Revise** for factualness. What is "*first wave*"? This sentence describes "classic" genome editing for a specific application, not "first-wave" synthetic biology.	Comment noted, revision made

IWF	25	27	Formatting error between line 26 and 27	comment noted
CDTBE-UK	25	33	Doesn't make sense – maybe 'conversion of the industrial…'	Editorial suggestions noted and revisions made.
IWF	25	33	The sentence needs reframing to be clearer.	Editorial suggestions noted and revisions made.
Global Youth Biodiversity Network-Uganda	25	33	and the conversion of the industrial yeast Pirichia pastoris from a heterotroph into an autotroph	Editorial suggestions noted and revisions made.
Global Industry Coalition	25	10-12	**Revise** for factualness. The introductory sentence does not make sense, and it is not true. This can be stated more factually and clearly, e.g. "*Metabolic engineering aims to optimise biological production of biochemicals."*	Editorial suggestions noted and revisions made.
Expert committees of DFG	25	42-43	A correction to the South et al. (2019) reference given here has been published; it appears the statistically supported gain in biomass is less than 40%. Needs updating.	Editorial suggestions noted and revisions made.
CDTBE-UK	26	22	And now Sars-CoV-2 (https://doi.org/10.1038/s41586-020-2294-9). The benefits/reasoning of synthesising these specific viruses could be mentioned (e.g. vaccine development), to give context as to why dangerous viruses might be produced in the first place.	Revision made.
CDTBE-UK	27	23	The authors could make a mention of microfluidics here.	Comment noted and Revision made.
CDTBE-UK	27	24	It's not clearly stated that Xenobiology could aid the biocontainment of new synthetic organisms by ensuring that they don't share the same genetic code with naturally-derived organisms. In this way, xenobiology could help the development of separate chassis specialised for research that cannot replicate if they escape into the environment due to this fundamental genetic incompatibility. This strategy could allow for research into genetically	Comment noted.

			distinct organisms that have different ways of storing information, suggesting that they do not pose a risk to the environment if escape does take place.	
Expert committees of DFG	27	29	Why to include xenobiotics in the context of CBD? These eventual products will be orthogonal organisms not posing any ecological threat.	Revision made.
GJSG on SynBio	27	29	Xenobiotic strains will be orthogonal organisms not posing any ecological threat.	Revision made.
Global Industry Coalition	27	30	**Revise** for factualness. The statement that "*xenobiology is the study of unusual life forms*" needs to be edited.	Revision made.
Expert committees of DFG	27	01-05	What is the rationale for considering protocells or minimal cells in the context of CBD? They are per definition and construction non-living systems as stated in the text.	See scope and methods,
GJSG on SynBio	27	01-05	Protocells and minimal cells in are, with regard to their dependence on other cells and cell components, non-living systems as stated in the text.	See scope and methods.
Max Planck Institute for Terrestrial Microbiology	27	01 ff	Unclear, why protocells and/or cell-free systems are classified as synthetic biology, also unclear why these systems are considered in the context of CBD, as they do not replicate and/or evolve.	See scope and methods.
EBRC	27	24-28	Recommend the addition of a Build a synthetic Cell consortium (BaSyC https://www.basyc.nl/-) and EU Synthetic Cell initiative https://www.syntheticcell.eu/	Revision made.
CDTBE-UK	28	25	A real-world application is not provided. This could be a reference for the CETCH cycle, the first fully synthetic and possibly the most efficient way of capturing CO2 in vitro. It makes use of 17 enzymes from all 3 domains. Expressing enzymes from different domains of life in a single host is incredibly challenging, yet, by making the enzymes work in tandem in vitro, the CO2 capture was more efficient than any of the 6 natural CO2 fixation pathways known. (DOI: 10.1126/science.aah5237)	Comment noted.

IWF	28	25	The case studies or examples of any live research/project can be provided to concretely backup the argument.	Revision made.
Global Industry Coalition	28	25	**Replace** "*cocktail of chemicals*" with "*conditions to survive*"	Editorial suggestions noted and revisions made.
UK EBLC	28	29	Whilst it is true that cell-free systems can contribute in several ways to improving the design process in synthetic biology, a key point is that this approach is likely to be important in relation to a range of biologically based manufacturing processes.	comment noted
Expert committees of DFG	28-29	28-10	What is the rationale for considering cell-free technologies in the context of CBD? These are non-living systems, even under the most lenient definitions of life and do not have the ability to replicate. Possibly relevant to digital sequence information (as a code base for in vitro produced proteins), hence already covered in this sphere.	See scope and methods.
GJSG on SynBio	28-29	28-10	Cell-free technologies provide non-living systems, unable to replicate and thus not relevant in the context of regulation.	see scope and methods.
PRRI	29-41		With an unclear definition of Synthetic Biology the examples given are meaningless, as they are not always synthetic biology. Some are LMOs, some are mutations as we find within normal variability (and considered Precision Breeding/New Breeding Techniques).	Revision made
Global Industry Coalition	29	12-15	**Revise** for factualness. A more factual representation of these sentences would be: "*The advances in biotechnological tools and techniques since the late 20th century have provided a diverse toolbox for practitioners for a range of potential applications and products. This section describes specific examples and is not an exhaustive list*.". Synthetic biology does not provide an "unprecedented toolbox" and it should be noted that the many of the examples given subsequently should not be classified as synthetic biology.	Editorial suggestions noted and revisions made.

Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	29	17-25	While it is certainly true that some applications of gene drives are intended for use in "unmanged/wild settings" (see e.g. Simon et al 2018) the use of different environmental settings as categories are not unambiguously assignable for some applications, as those would affect multiple categories. Simon, Samson; Otto, Mathias; Engelhard, Margret (2018): Synthetic gene drive: between continuity and novelty. Crucial differences between gene drive and genetically modified organisms require an adapted risk assessment for their use. In: EMBO reports (5). DOI: 10.15252/embr.201845760.	comment noted
Global Industry Coalition	30	02	We agree with the authors in their labelling of bacteria as genetically engineered, which underlines the point that not all examples provided in the text can, or should be classified as synthetic biology.	comment noted
JCVI	30	12	Rather than the term "xenobiotic cleanup", Rylott and Bruce refer to clean-up of environmental pollutants or clean-up of "inorganic and organic pollutants".	Revision made
Global Industry Coalition	30	27	"*Synthetic biology applications*" is used misleadingly as an umbrella term of any development in biotechnology.	Revision made
Global Industry Coalition	30	30	**Delete** "*use*" and **replace** with "*potential application*".	Revision made.
JCVI	30	35	The gene-drive developed for mice was to help develop medical mouse models and would not work for a biocontrol application.	Revision made
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	30	39	"heritance" should probably read "inheritance"	Editorial suggestions noted and revisions made.
Global Industry Coalition	30	42	**Delete** "*Synthetic biology is currently being applied to conservation (Piaggio et al., 2017). In ocean ecosystems…*" and **replace with**, "*The potential for synthetic biology in conservation applications is currently being investigated, for example in ocean ecosystems.*"	Editorial suggestions noted and revisions made.

JCVI	30	2-26	The bioremediation, biodegradation, and biomining examples would be better placed in the semi-managed/managed section that follows, rather than wild settings	Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	30	27/41	Those two headlines consider overlapping issues, as "conservation purposes" and "improving resilience of wild animal and plant populations" can subsume identical lines of research.	Revision made
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	30	27/41 f.	Use of (transmissible) viruses and engineered derivatives has been discussed for biocontrol of zoonoses and vaccination purposes in wild populations (Murphy et al. 2016, Bull et al. 2018). Please consider to check the status of research of engineered viruses and eventually amend the respective chapters. Bull, James J.; Smithson, Mark W.; Nuismer, Scott L. (2018): Transmissible Viral Vaccines. In: Trends in microbiology 26 (1), S. 6–15. DOI: 10.1016/j.tim.2017.09.007. Murphy, Aisling A.; Redwood, Alec J.; Jarvis, Michael A. (2016): Self-disseminating vaccines for emerging infectious diseases. In: Expert review of vaccines 15 (1), S. 31–39. DOI: 10.1586/14760584.2016.1106942	Revision made.
Global Industry Coalition	30	28-29	**Delete** "*island communities*" and **replace** with "*indigenous species on islands*".	Editorial suggestions noted and revisions made.
Expert committees of DFG	30	36-40	Not a synthetic biology application and not a gene-drive system.	comment noted
WHO	30		· Propose that the authors review the OPCW Scientific Advisory Board (SAB) reports on implications of S&T developments. See https://www.opcw.org/resources/documents/subsidiary-bodies/scientific-advisory-board	General comment noted
Global Industry Coalition	31	03	**Delete** "*Terrestrial organisms are also being subjected to research.*" And **replace** with "*Applications for terrestrial organisms are also being examined.*"	Editorial suggestions noted and revisions made.

PRRI	31	14	Change from commercially available to approved for commercial release, because some products that were approved for commercial release are not commercialized.	Editorial suggestions noted and revisions made.
CDTBE-UK	31	18	A comment on the positive impact of this example specifically: the resulting high oleic oils contain no trans fats and less saturated fats (both drivers of increased risk of heart disease). (https://calyxt.com/first-commercial-sale-of-calyxt-high-oleic-soybean-oil-on-the-u-s-market/)	Revision made.
CDTBE-UK	31	23	A much-improved approach over using synthetic nitrogen fertilizer; this leads to soil degradation and acidification, nitrous oxide emissions and nitrogen leaching in groundwater, streams, estuaries and coastal waters. Again, the context of why to use synbio technologies over current approaches is important.	comment noted
PRRI	31	27	*Self-limiting insects (Oxitec)* are LMOs and went through the regulatory process as such *they gained approval for commercial release in Brazil but are not commercialized ….*	Revision made
ETC Group	31	27	As written the statement implies that a company (Oxitec) has developed a self-limiting GM mosquito, when, in reality, this is still at the experimental stage, with several unpredicted effects reported and no benefits yet demonstrated.	Revision made.
African Centre for Biodiversity	31	27	This statement implies that Oxitec has developed a self-limiting GM mosquito, when this is in fact still at the experimental stage, with several unpredicted effects reported and no benefits yet demonstrated.	Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	31	28	Consider replacing “developed” by “genetically modified”	Comment noted.

Third World Network	31	30	References showing commercial approval of each of these insects are lacking. We suggest this is clarified and substantiated with references to all the species listed, otherwise they should be removed entirely from this section.	Revision made.
Global Industry Coalition	31	33	**Revise** for factualness. None of the examples described in Section 3.2.2 (a) can be claimed to be synthetic biology. They are examples of products that are similar to conventional ones. “Advanced Development” is not true for all of the examples that follow. It would be more correct to say "In development" for some, and others belong in the "research" section. "Advanced" implies it is not far from "commercially available" (the category above). None of the gene drive examples are "advanced", even the most developed applications are years from field testing. The agricultural example was a proof of concept (research).	See scope and methods.
Third World Network	31	36	The statement that “Menz et al. (2020) have recently reviewed and estimated that 140 genome-edited cultivars of 36 crops that improve yields, nutrition, and pest resistance, are already under development” is incorrect. This review does not list pest resistant varieties. The review criteria for identifying ‘marketable crops’ did not include evidence of trait efficacy, but evidence of genetic modification of a trait. The review also includes proprietary crops, despite no publicly available data on efficacy to assert such claims. The review states that many of the crops are in preliminary research stages. Given the information provided by Menz et al., (2020), the sentence should be corrected to reflect that traits improving yield, nutrition or pest resistance are in development e.g. the sentence could be modified to: “Menz et al., (2020) have recently reviewed and estimated that 140 genome-edited cultivars of 36 crops that aim to improve yields, nutrition, and pest resistance, are already under development, though evidence of efficacy remains to be substantiated.”	Revision made.
ETC Group	31	36	The Menz (2020) study the paper cites itself suggests that the claims of those producing the cultivars have yet to be substantiated, yet the success of the technique is stated as fact. Given the information provided by Menz et al.,	Revision made.

			(2020), the sentence should be corrected to reflect that traits improving yield, nutrition or pest resistance are in development e.g. the sentence could be modified to: "Menz et al., (2020) have recently reviewed and estimated that 140 genome-edited cultivars of 36 crops that aim to improve yields, nutrition, and pest resistance, are already under development, *though evidence of efficacy remains to be substantiated*."	
African Centre for Biodiversity	31	36	The Menz (2020) paper states that the claims of those producing the cultivars have yet to be substantiated, yet here the success of the technique is stated as fact. The sentence could be modified to: "Menz et al., (2020) have recently reviewed and estimated that 140 genome-edited cultivars of 36 crops that ***aim*** to improve yields, nutrition, and pest resistance, are already under development, ***though evidence of efficacy remains to be substantiated."***	Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	31	36	Yield increase can be challenging to determine robustly under relevant conditions. Please consider rephrasing "improve" by "aim to improve"	Revision made
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	36	38	Please consider to define the meaning of "advanced development" for (genome edited) farm animals to clarify the developmental status.	Revision made
Global Industry Coalition	31	14-32	**Revise** for factualness. The examples provided in Section 3.2.1 should be removed as none of these can be claimed to be examples of synthetic biology. For example, in lines 24-26 a product is referred to that contains a point mutation which is clearly not synthetic biology. The outcome is a trait that **already exists** as it can arise via mutation using conventional (non-biotech) tools.	See scope and methods and section 3.
ISF	31	14-40	Examples provided in sections 3.2.1 and 3.2.2 are not examples of synthetic biology but again examples of applying genome editing as targeted mutagenesis. For example, lines 24-26 refer to a point mutation that may not even have been caused by genome editing but be a result of somaclonal variation. Moreover, the same trait can be and has been obtained by	See scope and methods and section 3.

			conventional breeding. Examples provided in these chapters are misleading and need to be deleted.	
PRRI	31	15-26	*Genome edited soya bean (Calyxt) and Genome edited oilseed rape tolerant to herbicides (Cibus)* are examples of mutagenesis, they are examples of Precision Breeding or New Breeding Technique, not a Synthetic biology product.	See scope and methods and section 3.
Expert committees of DFG	31	24-26	Recent data indicates that this mutation was not obtained by ODM but is rather a spontaneous mutation that arose during tissue culture. Certainly not an example for synthetic biology (point mutations, no foreign DNA etc), because an identical trait achieved by selection for naturally occurring mutations is marketed by BASF under the trade name "ClearField". Both Cibus and Clearfield oil seed rape would have identical properties w/r to herbicide tolerance, one would be considered as synthetic biology, the other one not.	See scope and methods and section 3.
GJSG on SynBio	31	24-26	Certainly not an example for synthetic biology (point mutations, no foreign DNA etc). An identical trait achieved by selection for naturally occurring mutations is marketed by BASF.	See scope and methods and section 3.
JCVI	31	27-32	Unless there is a very recent change, Oxitec insects are still in advanced development stage (as listed on page 32) or research. I am not aware that Oxitec mosquitos can be commercially purchased and other insects are in earlier stages of development.	Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	31	33 f	General comment on section 3.2.2 The term "advanced development" should be precisely defined, not only for plants, but for all kinds of applications in this section. For plants, it should further be specified if applications in these sections stand for developmental/market trends or for examples for new traits. Currently, without further explanation the choice of examples such as for genome edited or classical genetically engineered plants appears arbitrary to a certain extent. Especially, in the context that a major part of plants likely to reach the market	Revision made.

			in the near future harbour traits conferring insect or herbicide resistance – such as the already marketed canola (Cibus).	
WHO	31	Section 3.2.1.d (and page 32 line 5)	· Possible WHO input vis-à-vis genetic modification of mosquito policy. See https://www.who.int/news/item/14-10-2020-who-takes-a-position-on-genetically-modified-mosquitoes and related]	The WHO report is considered in the subsections about policy
PRRI	31-32	33-04	This number of genome edited cultivars is misleading as they are not referring to Synthetic Biology alone, but to modern biotechnology and precision breeding/New Breeding Techniques mixed together.	comment noted.
Expert committees of DFG	31-32	34-4	Most crop plant examples listed here should not be considered "synthetic biology", most carry single base mutations or small deletions/insertions. The criterion "made with CRISPR/Cas9" would not render these synthetic biology products in any way and in several major markets they would not be regulated as GMOs anyway.	See scope and methods.
GJSG on SynBio	31-32	34-4	Most crop plant examples listed here should not be considered "synthetic biology", most carry single base mutations or small deletions/insertions. Products "made with CRISPR/Cas9" would not be regulated as GMOs in several major markets.	See scope and methods.
Global Industry Coalition	32	07	**Insert** "*one that confers*" after "*modifications*".	Editorial suggestion noted and revision made
Global Industry Coalition	32	07	**Insert** "*another that confers*" before *"The ability*".	Editorial suggestion noted and revision made
Global Industry Coalition	32	08	**Delete** "*wild*".	Editorial suggestion noted and revision made
Global Industry Coalition	32	08	**Revise** for factualness. "*advanced stage*" suggests that unrestricted releases are imminent - this is not the case. It would be more accurate to state that	Revision made.

			research has thus far been conducted in containment and may advance to field-releases in the foreseeable future.	
Imperial College London	32	11	Target Malaria has not done any field trials with gene drive mosquitoes. All gene drive strains are still under development and assessment in a contained facility. Therefore the following sentence "Similar initiatives are also underway but in contained conditions." Should be deleted.	Revision made.
Global Industry Coalition	32	11	**Revise** for factualness. The use of "*but*" is incorrect since the previous example is also in contained conditions.	Revision made
CDTBE-UK	32	15	This misses a comment on current casualty numbers associated with vector-borne diseases (in 2019: 5.2M cases of dengue, 229M malaria, 40.000 of zika). This is an important context that could justify the targeting of a small and limited number of mosquito species.	Comment noted.
Global Industry Coalition	32	18	**Replace** "*wild population*" with "*wild-type".*	Revision made
JCVI	32	20	Inaccurate heading for this section. "genetically engineered insects for biocontrol" or "self-limiting insects" as on the previous page.	Revision made
Western Michigan University	32	20	This section should also reference newer Oxitec technology. The self-limiting technology still constitutes a bio-contained system because the transgenics do not survive after a few generations.	Revision made
Global Industry Coalition	32	20	**Revise** for completeness. This section should reference more recent Oxitec technology. The self-limiting technology still constitutes a bio-contained system because the transgenic insects do not survive after a few generations.	Revision made
Third World Network	32	26	The statement that "progeny die in the absence of the dietary additive" ignores unintended effects of genetic engineering. Evans et al., (2019) showed introgression of OX513A into wild populations, building on the observation that 3-4 % survive in lab conditions without the presence of the dietary additive (Phuc et al., 2007), but survival could also be higher if the	Revision made

			additive is present in the environment (Patil et al., 2012). Such simplifications bias the reader to give the impression that such technologies do not suffer demonstrated inadequacies that warrant careful scrutiny under any assessment or regulatory process. We suggest this can be altered to accurately reflect the evidence to date: "After release into the field, the technology is designed to cause the progeny die in the absence of the dietary additive, however, sterility has been demonstrated to be incomplete in some RIDL systems, warranting precaution regarding potential unintended introgression and persistence in wild populations. Evans, B.R., Kotsakiozi, P., Costa-da-Silva, A.L. et al. Transgenic Aedes aegypti Mosquitoes Transfer Genes into a Natural Population. Sci Rep 9, 13047 (2019). https://doi.org/10.1038/s41598-019-49660-6 Phuc HK, Andreasen MH, Burton RS, Vass C, Epton MJ, et al. (2007) Late-acting dominant lethal genetic systems and mosquito control. BMC Biology 5: 11. doi:10.1186/1741-7007-5-1. http://www.biomedcentral.com/1741-7007/5/11 Patil P et al. (2012) Discussion on the proposed hypothetical risks in relation to open field release of a self-limiting transgenic Aedes aegypti mosquito strains to combat dengue. As. Pac. J. Mol. Biol. & Biotech., 18(2), 241–246.	
African Centre for Biodiversity	32	26	The statement that "progeny die in the absence of the dietary additive" ignores unintended effects of genetic engineering. Evans et al., (2019) showed introgression of OX513A into wild populations, building on the observation that 3-4 % survive in lab conditions without the presence of the dietary additive (Phuc et al., 2007), but survival could also be higher if the additive is present in the environment (Patil et al., 2012). Such simplifications bias the reader to give the impression that such technologies do not suffer demonstrated inadequacies that warrant careful scrutiny under any assessment or regulatory process. We suggest this can be altered to accurately reflect the evidence to date: "After release into the field, the technology is designed to cause the progeny die in the absence of the dietary additive, however, sterility has been demonstrated to be incomplete in some RIDL systems, warranting precaution	Revision made

			regarding potential unintended introgression and persistence in wild populations. Evans, B.R., Kotsakiozi, P., Costa-da-Silva, A.L. et al. Transgenic Aedes aegypti Mosquitoes Transfer Genes into a Natural Population. Sci Rep 9, 13047 (2019). https://doi.org/10.1038/s41598-019-49660-6 Phuc HK, Andreasen MH, Burton RS, Vass C, Epton MJ, et al. (2007) Late-acting dominant lethal genetic systems and mosquito control. BMC Biology 5: 11. doi:10.1186/1741-7007-5-1. http://www.biomedcentral.com/1741-7007/5/11 Patil P et al. (2012) Discussion on the proposed hypothetical risks in relation to open field release of a self-limiting transgenic Aedes aegypti mosquito strains to combat dengue. As. Pac. J. Mol. Biol. & Biotech., 18(2), 241–246.	
Outreach Network for Gene Drive Research	32	05-19	As mentioned elsewhere, neither "engineered gene drives in mosquito for potential control of vector-borne diseases" or "engineered gene drive for an agricultural pest" are considered to be in "advanced development".	Revision made.
Outreach Network for Gene Drive Research	32	09-11	This language is potentially misleading as it implies that Target Malaria's work is not conducted in contained conditions. It should be rephrased to make clear that all of Target Malaria's research to date involving organisms with engineered gene drives takes place in containment, and no field testing of a gene drive system has been undertaken or is planned for the near future. (Target Malaria did perform a small-scale release of genetically modified mosquitoes in Burkina Faso in 2019, but they did not contain gene drives. For more information: https://targetmalaria.org/results-from-months-of-monitoring-following-the-first-release-of-non-gene-drive-genetically-modified-mosquitoes-in-africa/)	Revision made
Third World Network	32	14-15	The statement that Adolfi et al., (2020) have improved CRISPR/Cas in mosquitoes "resulting in" populations resistant to transmitting malaria is entirely incorrect. The study did not test the resistance to the pathogen but instead exmined the efficiency of a population modification gene drive rescue strategy in small cage trials. It remains to be demonstrated if population	Revision made.

			modification strategies are indeed refractory to malaria parasites or other pathogens. As such, *we recommend that this sentence and reference be removed*. Accurate benefit-risk analysis is vital when considering the development of these new technologies. We urge that any potential yet-to-be established benefits are not conflated with demonstrable efficacy.	
African Centre for Biodiversity	32	14-15	The statement that Adolfi et al., (2020) have improved CRISPR/Cas in mosquitoes "resulting in" populations resistant to transmitting malaria is incorrect, as the study did not test the resistance to the pathogen. It remains to be demonstrated if population modification strategies are indeed refractory to malaria parasites or other pathogens. As such, **we recommend that this sentence and reference be removed.** .	Revision made.
Imperial College London	32	20-33	It might be good to reference Oxitec here	Comment noted.
Expert committees of DFG	32-33	39-2	Description seems odd – how can knockout lines of genes encoding a receptor be transformed into a rape-seed cultivar? Was genome editing used to achieve the knockout in the strigolactone receptor in the rapeseed cultivar Westar? In any case, knockout of a particular gene can also be achieved by undirected (random) mutagenesis, albeit with less precision and hence more potential risk. The resulting cultivar would nevertheless not be considered a regulated GMO and not a synthetic biology product. Another case for confusing targeted mutagenesis with synthetic biology, a theme that runs throughout the entire document.	comment noted
Expert committees of DFG	32-33	39-2	Apparently a naturally-occurring partial loss-of-function allele of strigolactone pathway underpins Green Revolution elite rice cultivars. To cite from the Stanic et al (2020) paper "Recently, it has been shown that specific SL partial loss-of-function alleles were also artificially selected for, along with GA mutant alleles, in the generation of elite dwarfed rice varieties during the green revolution (Wang et al., 2020)." I.e., a very substantial portion of the population is consuming products derived from plants that carry the same genetic feature, without ever being considered as synthetic	comment noted.

			biology products. Another case for arguing with the means of production, rather than considering the actual product.	
GJSG on SynBio	32-33	39-2	Targeted mutagenesis is confused with synthetic biology throughout the document: The knockout of a particular gene can also be achieved by random mutagenesis, however, with less precision and more potential risk. The resulting cultivar neither is a GMO nor a synthetic biology product.	comment noted.
CDTBE-UK	33	10	Extra space and space missing (2019) recently …'	Editorial suggestions noted and revisions made.
CDTBE-UK	33	16	This could reduce the need for synthetic fertilisers, the dangers of which we have commented on.	Comment noted.
Iowa State University	33	22	The first Insect Allies publication was not the Ellison et al. 2020 paper. It was most likely "Mei et al. 2019. Mei, Y., Beernink, B. M., Ellison, E. E., Konečná, E., Neelakandan, A. K., Voytas, D. F., Whitham, S. A. (2019) Protein expression and gene editing in monocots using foxtail mosaic virus vectors. Plant Direct. 3:e00181. doi: 10.1002/pld3.181". Mei et al. 2019 investigates use of a virus for somatic protein expression and somatic gene editing in model plants and maize.	Revision made
Iowa State University	33	31	Arabidopsis is misspelled	Editorial suggestions noted and revisions made.
JCVI	33	33	Incomplete heading. Section includes both "de-extinction" and applications to species close to extinction (though these are cloning). In addition to Przewalski's foal, you might also include the recent example of cloning to increase the genetic diversity of black-footed ferrets.	Revision made
WHO	33	35	Suggest "By 2018, there were" read: "By 2018, there were at least"	Revision made
Max Planck Institute for Terrestrial Microbiology	33	13 ff	"Synthetic" microbial communities do not necessarily involve the use of modified microbes, but typically the defined composition of a microbial	Revision made

			community from naturally existing strains. Usually no synthetic biology or genetic engineering involved.	
Expert committees of DFG	33	13-16	What is called “synthetic beneficial microbiota” does usually not involve any genetic engineering, but rather an inoculum consisting of selected, naturally-occurring bacterial strains (synthetic microbial community or SynCom). Has nothing to do with synthetic biology, despite the (confusing) use of the word “synthetic”.	Revision made.
GJSG on SynBio	33	13-16	“Synthetic beneficial microbiota” usually means consortia of naturally-occurring bacterial strains (synthetic microbial community). It has nothing to do with genetic engineering or synthetic biology, despite the use of the word “synthetic”.	Revision made.
JCVI	33	17, 18	Again, inaccurate heading. None of the papers cited have anything to do with insect delivery. These are examples of virus vectors for genome editing used in the lab. The notion of HEGAAs is an attention-getting headline but implying that the examples listed are “environmental agents” is quite misleading. It is also a bit odd to me that 50% more text is devoted to viral agents for genome editing than CRISPR edited plants and animals on p.31 and 32.	Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	33	17-32	HEGAAs are a relevant example for Synthetic Biology in the field of GM Viruses, but please also consider discussing the example of transgenic viruses to combat “citrus greening” as it is both relevant and comparably close to marketing.	Revision made.
Iowa State University	33	19-32	Tobacco rattle virus (TRV) is not insect transmitted (transmitted by nematodes). In the engineered TRV vector, the open reading frames required for nematode transmission are deleted. Potato virus X (PVX) is not known to be insect transmitted.	Revision made.
Iowa State University	33	25-32	The Ariga et al. 2020 and the Ma et al. 2020 studies both required regeneration of infected plants through tissue culture in order to produce edits	Revision made.

			that were inherited. This is a very cumbersome and technically demanding process.	
Iowa State University	33	25-32	A more recent paper from a Spanish group uses PVX as a vector to deliver guide RNAs and produce Nicotiana benthamiana plants carrying heritable edits by two different methods. 1. They regenerate plant through tissue culture similar to Ariga et al. 2020 and Ma et al. 2020. 2. They directly induce heritable edits by delivering a single guide RNA fused to the FT sequence by a strategy similar to Ellison et al. 2020. Both methods still require the use of Cas9 expressing transgenic Nicotiana benthamiana lines in which to deliver the guide RNAs. The paper is: Uranga, M., Aragonés, V., Selma, S., Vázquez-Vilar, M., Orzáez, D. and Daròs, J.-A. (2021), Efficient Cas9 multiplex editing using unspaced sgRNA arrays engineering in a Potato virus X vector. Plant J, 106: 555-565. https://doi.org/10.1111/tpj.15164.	Revision made.
Expert committees of DFG	34-37	34-19	Many of the examples included are not synthetic biology products but the result of typical classical genetic engineering/biotechnological approaches, e.g. recombinant proteins. In addition, most of these products should however not fall into CDB mandate, the method of production is considered and not the product itself which is indistinguishable from the natural or chemically synthesised compound. See above for “vainillin.”	See scope and methods.
GJSG on SynBio	34-37	34-19	Many of the examples are the result of typical classical genetic engineering/biotechnological approaches. Most of these products should not fall into CDB mandate, as they are indistinguishable from the natural or chemically synthesised compounds.	See scope and methods.
Expert committees of DFG	34	08	These are transient modifications, non-inheritable.	See scope and methods.
GJSG on SynBio	34	8	These are transient, non-inheritable modifications.	See scope and methods.
JCVI	34	8	Incomplete heading. I believe several of the examples are RNA pesticides that act directly on agricultural pests.	Revision made.

Global Industry Coalition	34	08	**Revise** for factualness. *"Transient modification of agricultural plants through RNAi spray or nanomaterials*" – this is not an example of synthetic biology. There is no description about what "nanomaterials" the authors refer to or why the authors have identified the application of RNA as an example of synthetic biology. The authors should note that another regulatory forum, under the OECD is addressing the regulation of such future products.	Comment noted.
Max Planck Institute for Terrestrial Microbiology	34	08	Describes transient modifications	See scope and methods.
CDTBE-UK	34	29	'described a synthetic biology …' not 'an synthetic …'	Editorial suggestions noted and revisions made.
IWF	34	29	'an' should be replaced by 'a' before synthetic	Editorial suggestions noted and revisions made.
JCVI	34	34	Several of the examples in the following 2.5 pages are more accurately described as advanced development. I will point out a few, but I think the authors should reconsider their definition of "commercially available" to include some notion of commercially viability rather than just proof of concept.	Revision made.
Third World Network	34	17-18	"Each example is an important first step towards developing practical applications of this approach in crop protection". We suggest deleting this sentence, as stating this without the corollary, that there are also potential adverse effects that need to be assessed and regulated, creates an impression of bias.	Revision made.
African Centre for Biodiversity	34	17-18	The statement ""Each example is an important first step towards developing practical applications of this approach in crop protection" as is should be deleted as it creates an impression of bias, as it does not state the potential adverse effects need to be assessed and regulated, at each step.	Revision made.

Global Industry Coalition	34	27-28	**Revise** for completeness. Why is *"Genetically engineered plants to produce recombinant polyclonal antibodies against snake venom toxins.*" a standalone category?	Comment noted. See scope and methods.
EBRC	34	34 3.3.1	Recommend to add synthetic biology-enabled vaccine production (in particular COVID vaccines) to this section	Revision made.
EBRC	34	34 3.3.1	Recommend to add enzymes for diverse applications (industrial, detergents, feed, food etc.) considering their significant impact on process footprints.	Revision made.
JCVI	34, 35	43	Cellbricks are cell scaffolds, not synthetic biology	Revision made
CDTBE-UK	35	9	'to be active' or ' to become activated upon …'	Editorial suggestions noted and revisions made.
EBRC	35	21	Recommend splitting the examples of Global Bioenergies and LanzaTech as these are fundamentally different. Global Bioenergies approach of fermenting sugar hydrolysates from plant waste (glucose and xylose from wheat straw; e.g. https://www.global-bioenergies.com/first-production-of-isobutene-from-wheat-straw-at-demo-scale) is distinct from that of LanzaTech. LanzaTech utilizes gasesous substrates which can come from gasified biomass in addition to other sources of waste gases (e.g. industrial off-gas, gasified municipal solid waste), e.g. https://doi.org/10.1016/j.copbio.2020.02.017	Comment noted.
CDTBE-UK	35	27	Should be a space between line 26 and line 27.	Editorial suggestions noted and revisions made.
WHO	35	7-11	Possible inputs regarding COVID-19 vaccine development and production.	Revision made.
JCVI	35	16-31	I believe most (if not all) of these applications should be moved to "advanced development"	Revision made
EBRC	35	33-35	Mango materials uses natural, non-genetically modified microbes. (link)	Revision made

CDTBE-UK	36	5	Should be a space between 'to' and 'melting'	Editorial suggestions noted and revisions made.
Expert committees of DFG	36	16	It is unfounded to expand the CBD mandate to synthetised , in vitro produced DNA?	Comment noted.
GJSG on SynBio	36	16	There is no need to extend the CBD mandate to DNA synthesized in vitro.	Comment noted.
CDTBE-UK	36	38	Higher Steaks also do this: https://www.highersteaks.com/about-us	Revision made.
JCVI	36	31-36	Advanced development more appropriate?	Revision made
JCVI	37	12-19	Advanced development more appropriate?	The product is available for purchase at the developer webpage
CDTBE-UK	38	7	Should be a space '… disorders. One …'	Editorial suggestions noted and revisions made.
Expert committees of DFG	38	22	Protocells are not living organisms (see above).	comment noted
GJSG on SynBio	38	22	Protocells are not living organisms (see above).	comment noted
EBRC	38	28	Recommend the addition of a Build a synthetic Cell consortium (BaSyC https://www.basyc.nl/) and EU Synthetic Cell initiative https://www.syntheticcell.eu/	Revision made.
WHO	38	01-20	Possible WHO inputs (e.g. prequalification of medicines procedures, including ethical dimension)	General comment noted
Max Planck Institute for Terrestrial Microbiology	38	22 ff	Protocells and/or viruses are not organisms	General comment noted
Expert committees of DFG	38	36-41	A virus is not to be considered as a microorganism.	Editorial suggestions noted and revisions made.

GJSG on SynBio	38	36-41	A virus is not a microorganism.	Editorial suggestions noted and revisions made.
JCVI	38	36-41	The heading should refer to the application: "Modified horsepox virus to use as a smallpox vaccine." The company is also researching use of the virus for a COVID-19 vaccine. It is fine to mention that it was re-created in the text, but not as the title. I do not understand the last sentence. There was no physical sample to work with.	comment noted.
CDTBE-UK	39	12	Missing word, should read '… prevent transfer of transgenic …'	Editorial suggestions noted and revisions made.
CDTBE-UK	39	23	Should be a space between ' … 2013) and 35 …'	Editorial suggestions noted and revisions made.
PRRI	39	01-15	There are different strategies being developed to increase safety within Synthetic Biology beyond kill-switches that should have been discussed, such as dependence on supplied nutrients for survival (e.g. unnatural amino acids) to quickly remove engineered organisms from the environment.	Revision made.
CDTBE-UK	40	01	Should be a space ' … 2020) reviewed …'	Editorial suggestions noted and revisions made.
CDTBE-UK	40	04	Should be a space ' … arsenic levels (Wan …'	Editorial suggestions noted and revisions made.
EBRC	40	24	Recommend addition of Global Alliance of Biofoundries	Revision made.
Global Industry Coalition	40	28	**Revise** for factualness. "*engineered gene drives to control vector-borne diseases"* are not advanced! They have progressed from "early stage" but cannot be "advanced" if they have not been tested outside of strict containment.	Revision made
Expert committees of DFG	40	05-17	See above example vainillin. Why to regulate such a product.	Revision made.
GJSG on SynBio	40	5-17	Regulation of products from synthetic biology approaches is pointless as they are no different from chemically synthesized compounds; biotechnologically produced vanillin is a prime example.	Revision made.

Global Industry Coalition	40	07-09	**Revise** for factualness. Lines 7-9 suggest that the number of commercially available and advanced stage synthetic biology applications has greatly increased. This statement must be supported by evidence. We recommend that the authors provide a table that compares information in the Technical Series document from 2015 and this new edition.	Revision made
EBRC	40	14-15	Calysta is neither specialized in algal biofuels nor sold/out of business (https://www.calysta.com). Unaware of any commercial algal biofuels currently on the market as indicated on page 35, lines 17-20. For example, Photanol shifted toward higher value molecules (https://photanol.com)	Revision made.
Global Industry Coalition	40	25-26	**Revise** for factualness or **delete**. None of the examples given are products of synthetic biology.	
Outreach Network for Gene Drive Research	40	26-28	As above, gene drives for disease vector control are not in the advanced stages of development.	Revision made.
Imperial College London	40	27-29	How is the advanced stage of development defined? All of the gene drive constructs to potentially control vector populations are still under research and development. There have been no field trials and more experiments are needed to assess these strains and other potential gene drive candidates.	Revision made.
JCVI	40	30-34	Perhaps this paragraph should have been included in the beginning of the Applications section, along with an explanation of the criteria used to distinguish “commercially available” from advanced development.	Revision made.
UK EBLC	40	35-36	Both computer-based cell design and biomaterials should also be considered within section D, which is instead mainly focused on genome editing.	Comment noted.
Expert committees of DFG	40	37-39	Not all these approaches involve gene drives. Throughout the whole section 4.1 a generalised used of “drives” is present, while this is not necessarily the	Comment noted.

			case for several/most of the applications which involve Mendelian inheritance molecular systems.	
Global Industry Coalition	41	08	**Replace** "*which are equally*" to "*which may be*". They are not "equal" - this is a generalisation. They vary in importance according to the priorities and circumstances of the jurisdiction.	Editorial suggestions noted and revisions made.
Western Michigan University	41	13	See my previous comments on this concept.	Editorial suggestions noted and revisions made.
Global Industry Coalition	41	13	**Delete** *"Although synthetic biology is often referred to as a coherent and single discipline,*" or define where it is referred to in this way. The "operational definition" used in this document is not consistent with this statement.	Revision made.
Imperial College London	41	13-15	Which is why it should not be regarded as single discipline	Revision made.
Global Industry Coalition	41	15-16	**Replace: "***In trying to describe such impacts, a multitude of factors need to be discerned.***"** with **"***Products developed using synthetic biology approaches, as with any product, may have potential impacts on the conservation and sustainable use of biological diversity and it is important to perform a risk assessment prior to their introduction to identify, and if necessary manage the risks which may occur. Similarly, the socio-economic impacts of a product of synthetic biology may be assessed as in any other case."*	Editorial suggestion noted.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	41	17/18	Comparing the aim of "suppression gene drives" and "chemical control agents" is misleading as the result can be very different depending on how it would be applied. Suppression drive might be designed to extinct a whole species, which might not be the achievable by chemical control agents.	Comment noted. Revision made.
Global Youth Biodiversity Network-Uganda	41	18	Some of such impacts will be specific to the host organism, while	Editorial suggestion noted.

CDTBE-UK	41	20	This is also target dependent. For instance, non-native and invasive species are unlikely to develop mutually beneficial bonds with other organisms in that niche, and therefore their removal is likely wholly beneficial to the rest of that environment.	Comment noted
CDTBE-UK	41	23	This is very true. However these costs need to be weighted by importance. For instance, there is a very real and measured mortality associated with vector borne diseases such as malaria that could be greatly reduced with this technology; is slow action based on the uncertainties presented here really justifiable?	Comment noted
Western Michigan University	41	25	This reinforces the idea introduced on p. 12, lines 34-38 of including benefits in the assessment of impacts when deciding on the deployment of a technology, and not merely a precautionary approach based on risk considerations only.	Comment noted.
Imperial College London	41	25	As phrased in the previous sentence, there are benefits associated with these applications. These should be considered when assessing the potential impact of the application on a case by case basis.	Comment noted.
African Centre for Biodiversity	41-44	35-Entire 4.1	In discussing the positive and negative impacts of gene drives, potential negative impacts on disease epidemiology have not been included, both as a result of efficacy failures/ unintended effects (Beisel and Boëte, 2013; Sirinathsinghji et al., 2019). It is vital that gene drive technologies are not incorrectly and simplistically framed as having only potential benefits on disease and having potential negative effects are limited to ecological impacts. Potential adverse effects on health, such as disease resurgence in the event of drive resistance development and population re-bound are even acknowledged by gene drive developers (James et al., 2020), and also raised in the WHO guidance materials (2021). Niche-replacement with other disease vectors, the development of increased pathogenicity in response to effector molecules in gene replacement drives, increases in vector competence and capacity are also potential outcomes. Many of the adverse effects cannot be assessed prior to release.	Comment noted.

			Wider ecological and social determinants are completely omitted, ranging from issues such as behavioural resistance; and impacts on wider social determinants of disease and existing treatments that may suffer opportunity costs from any narrow technological focus on disease interventions. Of note, China has been recently declared malaria free, based largely on access to free health services, surveillance and political coordination, demonstrating the importance of existing strategies in defeating vector borne disease. Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/ Beisel U and Boëte C (2013). The Flying Public Health Tool: Genetically Modified Mosquitoes and Malaria Control. Science as Culture, 22, 38-60. doi: 10.1080/09505431.2013.776364 James, S. L., Marshall, J. M., Christophides, G. K., Okumu, F. O. & Nolan, T. Toward the Definition of Efficacy and Safety Criteria for Advancing Gene Drive-Modified Mosquitoes to Field Testing. Vector-Borne Zoonotic Dis. 20, 237–251 (2020)	
ETC Group	41	Entire section 4.1	In discussing the positive and negative impacts of gene drives, potential negative impacts on disease epidemiology have not been included, both as a result of efficacy failures/ unintended effects (Beisel and Boëte, 2013; Sirinathsinghji et al., 2019). It is vital that gene drive technologies are not incorrectly and simplistically framed as having only potential benefits on disease, while potential negative effects are limited to ecological impacts. Potential adverse effects on health, such as disease resurgence in the event of drive resistance development and population re-bound are even acknowledged by gene drive developers (James et al., 2020), and also raised in the WHO guidance materials (2021). Niche-replacement with other disease vectors, the development of increased pathogenicity in response to effector molecules in gene replacement drives, increases in vector competence and capacity are also potential outcomes. Moreover, some of these adverse effects cannot be assessed prior to release. Wider ecological and social determinants	Comment noted.

			are completely omitted, ranging from issues such as behavioural resistance; and impacts on wider social determinants of disease and existing treatments that may suffer opportunity costs from any narrow technological focus on disease interventions. Of note, China has been recently declared malaria free, based largely on access to free health services, surveillance and political coordination, demonstrating the importance of existing strategies in defeating vector borne disease. Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/ Beisel U and Boëte C (2013). The Flying Public Health Tool: Genetically Modified Mosquitoes and Malaria Control. Science as Culture, 22, 38-60. doi: 10.1080/09505431.2013.776364 James, S. L., Marshall, J. M., Christophides, G. K., Okumu, F. O. & Nolan, T. Toward the Definition of Efficacy and Safety Criteria for Advancing Gene Drive-Modified Mosquitoes to Field Testing. Vector-Borne Zoonotic Dis. 20, 237–251 (2020).	
Third World Network	41	Entire section 4.1	In discussing the positive and negative impacts of gene drives, potential negative impacts on disease epidemiology have not been included, both as a result of efficacy failures/ unintended effects (Beisel and Boëte, 2013; Sirinathsinghji et al., 2019). It is vital that gene drive technologies are not incorrectly and simplistically framed as having only potential benefits on disease, while potential negative effects are limited to ecological impacts. Potential adverse effects on health, such as disease resurgence in the event of drive resistance development and population re-bound are even acknowledged by gene drive developers (James et al., 2020), and also raised in the WHO guidance materials (2021). Niche-replacement with other disease vectors, the development of increased pathogenicity in response to effector molecules in gene replacement drives, increases in vector competence and capacity are also potential outcomes. Moreover, some of these adverse effects cannot be assessed prior to release. Wider ecological and social determinants are completely omitted, ranging from issues such as behavioural resistance;	Comment noted.

			and impacts on wider social determinants of disease and existing treatments that may suffer opportunity costs from any narrow technological focus on disease interventions. Of note, China has been recently declared malaria free, based largely on access to free health services, surveillance and political coordination, demonstrating the importance of existing strategies in defeating vector borne disease. Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/ Beisel U and Boëte C (2013). The Flying Public Health Tool: Genetically Modified Mosquitoes and Malaria Control. Science as Culture, 22, 38-60. doi: 10.1080/09505431.2013.776364 James, S. L., Marshall, J. M., Christophides, G. K., Okumu, F. O. & Nolan, T. Toward the Definition of Efficacy and Safety Criteria for Advancing Gene Drive-Modified Mosquitoes to Field Testing. Vector-Borne Zoonotic Dis. 20, 237–251 (2020).	
Imperial College London	41	45	The gene drive applications under development for vector control will not be commercially distributed. The technology will be shared and will be deployed by government authorities or regional governing bodies with the aim to improve public health.	Revision made.
Global Industry Coalition	41	45	**Delete** "*have yet been commercialised*" and **replace** with "*are near deployment*"**.** The term "commercialisation" does not apply to all of the potential applications, as most will be for public good rather than "commercial" purposes.	Revision made.
WHO	41		2021 EU-level developments could be checked including with respect to biodiversity and GMOs	Revision made.
Imperial College London	42	01-02	Which is again why benefits should be included in a case-by case risk assessment.	Comment noted. See section 5.

CDTBE-UK	42	08	This is a critical point; the use of blanket synthetic pesticides has a demonstrably negative impact on biodiversity in the area used, with long term effect of their use still not clear. Compared to this status quo, at least a gene drive has a single intended target species, even if it's effects may be felt further along the food chain.	Comments noted, see section 5.
Imperial College London	42	17-20	These events are all hypothetical, and their relevance is construct specific.	Comment noted and revision made.
Western Michigan University	42	18-19	This phrase is confusing, since the subject of this section is Invasive Alien Species. It should be deleted.	Editorial suggestions noted and revisions made.
Global Industry Coalition	42	19	**Delete** "*is native or*" as this section is discussing IAS.	Editorial suggestions noted and revisions made.
Western Michigan University	42	20-23	These speculated impacts are case specific, and are not applicable to all gene edited organisms.	Comment noted and revision made.
Global Industry Coalition	42	20-23	Sentence refers to off-target mutations with genome editing. To present context and be more complete, it should also mention recent scientific reviews. For example, EFSA concluded that off target mutations are likely to be fewer in edited organisms that in conventionally bred organisms. EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), Naegeli H, Bresson J-L, Dalmay T, Dewhurst IC, Epstein MM, Firbank LG, Guerche P, Hejatko J, Moreno FJ, Mullins E, Nogue F, S anchez Serrano JJ, Savoini G, Veromann E, Veronesi F, Casacuberta J, Gennaro A, Paraskevopoulos K, Raffaello T and Rostoks N, 2020. Applicability of the EFSA Opinion on site-directed nucleases type 3 for the safety assessment of plants developed using site-directed nucleases type 1 and 2 and oligonucleotide-directed mutagenesis. EFSA Journal 2020;18(11):6299, 14 pp. https://doi. org/10.2903/j.efsa.2020.6299	Comment noted and revision made.

CDTBE-UK	42	22	Evolutionary resistance to a gene drive, especially CRISPR-Cas9 drives, is almost certainly expected after a period of time. Is that really a bad thing? This could act as a time or spatial limit to drive spread, while we benefit in the short term from the immediate effects of the drive before it is inactivated through evolution. Genomes are filled with transposable elements that became non-functional long ago in our evolutionary development; these are not really detrimental, but possibly lead to an increase in genetic diversity and genome stability. Gene drives that are inactivated due to non functional mutations will likely dilute out of the population over time as it provides no real advantage in fitness. It's unlikely that anything we develop with CRISPR-Cas9 will have the fidelity of the ancient transposases found throughout genomes, which universally acquire mutations and become stationary elements.	Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	42	23/24	The choice of references might be unbalanced here and could include e.g. Critical Scientists Switzerland et al., 2019; Dolezel et al., 2020 from lines 32/33 of the same page.	Comment noted. Revision made.
Third World Network	42	27	There is superfluous wording here that should be corrected for bias. It is currently premature to state that gene drives offer "genuine potential" for continental-wide eradication. It is generally accepted that gene drives will not completely eliminate mosquitoes, and some modelling suggests that releases will result in heterogeneous populations of wild-type and gene drive mosquitoes (e.g. North et al., 2020), even with regular releases. More recent data suggests that various ecological and climactic factors may have significant impacts on efficacy and remain understudied (Morris et al., 2021). Other issues, such as drive resistance, may also impede efficacy. It remains scientifically premature to state that they offer "genuine potential" for continental eradication. We suggest the sentence is corrected to reflect the uncertainty of gene drive efficacy as follows: "This approach is designed to increase the feasibility of large-scale control, though potential for continental- scale eradication of unwanted wild populations or species remains questionable, with potential for unintended effects such as drive resistance expected to impede eradication	Editorial suggestions noted and revisions made.

			efforts." North, A.R., Burt, A. & Godfray, H.C.J. Modelling the suppression of a malaria vector using a CRISPR-Cas9 gene drive to reduce female fertility. BMC Biol 18, 98 (2020). https://doi.org/10.1186/s12915-020-00834-z Morris, A.L., Ghani, A. & Ferguson, N. Fine-scale estimation of key life-history parameters of malaria vectors: implications for next-generation vector control technologies. Parasites Vectors 14, 311 (2021). https://doi.org/10.1186/s13071-021-04789-0	
African Centre for Biodiversity	42	27-28	This should be rephrased to avoid the incredible bias implicit in its current wording. At this stage, it is premature to state that gene drives offer "genuine potential" for continental-wide eradication. It is generally accepted that gene drives will not completely eliminate mosquitoes, and some modelling suggests that releases will result in heterogeneous populations of wild-type and gene drive mosquitoes (e.g. North et al., 2020), even with regular releases. More recent data suggests that various ecological and climactic factors may have significant impacts on efficacy and remain understudied (Morris et al., 2021). Other issues, such as drive resistance, may also impede efficacy. Therefore this statement is unscientific and unfounded. We suggest the sentence is corrected to reflect the uncertainty of gene drive efficacy as follows: "This approach is designed to increase the feasibility of large-scale control, though potential for continental- scale eradication of unwanted wild populations or species remains questionable, with potential for unintended effects such as drive resistance expected to impede eradication efforts." North, A.R., Burt, A. & Godfray, H.C.J. Modelling the suppression of a malaria vector using a CRISPR-Cas9 gene drive to reduce female fertility. BMC Biol 18, 98 (2020). https://doi.org/10.1186/s12915-020-00834-z Morris, A.L., Ghani, A. & Ferguson, N. Fine-scale estimation of key life-history parameters of malaria vectors: implications for next-generation vector control technologies. Parasites Vectors 14, 311 (2021). https://doi.org/10.1186/s13071-021-04789-0	Editorial suggestions noted and revisions made.

Third World Network	42	29	Island locations are not ecologically confined, and thus island releases also raise concerns regarding spread beyond site releases. The sentence erroneously conveys a notion that there is consensus regarding island locations being 'appealing' sites for release, when there is actually none. As recently acknowledged by the 2017 Synthetic Biology AHTEG: "Islands are not ecologically fully contained environments and should not be regarded as fulfilling the conditions in the definition of contained use as per Article 3 of the Cartagena Protocol unless it is so demonstrated."	Editorial suggestion noted and revision made.
ETC Group	42	29	Island locations are not ecologically confined, and thus island releases also raise concerns regarding spread beyond site releases. The sentence erroneously conveys a notion that there is consensus regarding island locations being 'appealing' sites for release, when there is actually none. As recently acknowledged by the 2017 Synthetic Biology AHTEG: "Islands are not ecologically fully contained environments and should not be regarded as fulfilling the conditions in the definition of contained use as per Article 3 of the Cartagena Protocol unless it is so demonstrated."	Editorial suggestion noted and revision made.
African Centre for Biodiversity	42	29	The sentence erroneously conveys a notion that there is consensus regarding island locations being 'appealing' sites for release, when there is actually none. As recently acknowledged by the 2017 Synthetic Biology AHTEG: "Islands are not ecologically fully contained environments and should not be regarded as fulfilling the conditions in the definition of contained use as per Article 3 of the Cartagena Protocol unless it is so demonstrated.". Island locations are not ecologically confined, and thus island releases also raise concerns regarding spread beyond site releases.	Editorial suggestion noted and revision made.
ETC Group	42	47	It is currently premature to state that gene drives offer "genuine potential" for continental-wide eradication. This wording should be corrected for bias. It is generally accepted that gene drives will not completely eliminate mosquitoes, and some modelling suggests that releases will result in heterogeneous populations of wild-type and gene drive mosquitoes, even with regular releases (e.g. North et al., 2020). More recent data suggests that various ecological and climactic factors may have significant impacts on efficacy that	Editorial suggestion noted and revision made

			remains understudied (Morris et al., 2021). Other issues, such as drive resistance, may also impede efficacy. It remains scientifically premature to state that they offer "genuine potential" for eradication across a continent. We suggest the sentence is corrected to reflect the uncertainty of gene drive efficacy as follows: "This approach is designed to increase the feasibility of large-scale control, though potential for continental- scale eradication of unwanted wild populations or species remains questionable, with potential for unintended effects such as drive resistance expected to impede eradication efforts." North, A.R., Burt, A. & Godfray, H.C.J. Modelling the suppression of a malaria vector using a CRISPR-Cas9 gene drive to reduce female fertility. BMC Biol 18, 98 (2020). https://doi.org/10.1186/s12915-020-00834-z Morris, A.L., Ghani, A. & Ferguson, N. Fine-scale estimation of key life-history parameters of malaria vectors: implications for next-generation vector control technologies. Parasites Vectors 14, 311 (2021). https://doi.org/10.1186/s13071-021-04789-0	
Imperial College London	42	31-33	This statement cannot be generalised as it is. The major advantage of a gene drive over conventional interventions against disease vectors is that it can spread and affect areas that cannot be easily assessed with existing vector control measures.	Comment noted.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	42	31-33	Those concerns are also raised for islands, as the escape might pose the risk of spread	Comment noted and revision made.
PRRI	42	34	No gene drives were released into the wild. Further, it does not matter whether they were developed using CRISPRs or develop through any other manner.	Comment noted.
Imperial College London	42	36-37	There are other interventions such as the widespread use of bednets and IRS that reduce mosquito populations and could have an impact on ecosystems. That risk is not unique to gene drives.	Comment noted.

Global Industry Coalition	42	37	**Replace** "*The most advanced application*" with "*the most advanced type of use of the technology*" is for malaria vector control".	Editorial suggestions noted and revisions made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	42	42/43	This is rather a simplification of the possible outcomes. Depending on the gene drive a construct could remain in the population for extended time frames (pulse chase dynamics) (Champer et al 2021), self-propagating suppression drives are seen as "highly invasive" (Esvelt and Gemmell 2017) J Champer, I Kim, SE Champer, AG Clark, PW Messer (2021). Suppression gene drive in continuous space can result in unstable persistence of both drive and wild-type alleles. Molecular Ecology. 30:1086	Comment noted, see section 6.
Imperial College London	42	44-46	That risk is construct and species dependent (how closely are species related to eachother and are they able to form fertile hybrids).	Comment noted and revision made.
Global Industry Coalition	42	45	**Replace** "*sibling*" with "*related*"	Editorial suggestion noted and revision made.
CDTBE-UK	43	02	"There is no evidence that (Evarcha culicivora) require Anopheles mosquitoes and will readily consume blood-fed Culex." from a more recent paper (doi:10.1111/mve.12327). This is important as drives will likely target one mosquito species per area at a time, while other species may take their place in the food chain. Although the identity and relative abundance of prey species may be different, biomass available to predators may not.	Revision made.
Global Industry Coalition	43	02-03	This is a generalisation that is inconsistent with the Collins paper referenced above (page 42 line 48) – this states that there is one predatory species with a specialisation on blood-fed mosquitoes including *A. gambiae –Evarcha culicivorais.* This jumping spider, known as the vampire spider, is found around Lake Victoria. There is no evidence that these salticids require *Anopheles* mosquitoes and will readily consume blood-fed *Culex*.	Revision made.
CDTBE-UK	43	04	This has been looked into for a long time, it appears that no species is significantly dependent on any one mosquito species alone.	Comment noted.

Imperial College London	43	04	There is a study by Collins et al which addressed this. Collins CM, Bonds JAS, Quinlan MM, Mumford JD. Effects of the removal or reduction in density of the malaria mosquito, Anopheles gambiae s.l., on interacting predators and competitors in local ecosystems. Med Vet Entomol. 2019 Mar;33(1):1-15. doi: 10.1111/mve.12327. Epub 2018 Jul 25. PMID: 30044507; PMCID: PMC6378608.	Revision made.
ZKBS	43	05-08	Ethically, the following sentence does not correspond to international values and should therefore be deleted: "Further, although not specific to synthetic biology approaches, the reduction or elimination of human malaria from geographical areas may lead to demographic and land-use changes, potentially impacting biodiversity conservation (Redford et al. 2019)".	Comment noted, and text revised.
CDTBE-UK	43	06	As mentioned, this could be done just as easily with an effective vaccine. Are we really weighing the human cost of malaria against potential changes in land use? This should be considered, but is not a justification against the use of this technology.	Revision made.
Western Michigan University	43	07-08	A relevant publication here is Collins, C. M., J. A. S. Bonds, M. M. Quinlan, and J. D. Mumford. "Effects of the Removal or Reduction in Density of the Malaria Mosquito, Anopheles gambiae s.l., on Interacting Predators and Competitors in Local Ecosystems." Medical and Veterinary Entomology 33, no. 1 (March 2019): 1–15. https://doi.org/10.1111/mve.12327.	Revision made.
Western Michigan University	43	15-20	These are not structurally different types of drive. Their effect (either suppression or replacement) depends upon the effector gene contained within the drive construct.	Comment noted and text revised.
Global Industry Coalition	43	22	Is this referring to replacing or providing an additional trait (as suggested in line 18)? Suggest revising: **Replace** "replace a population" with "replace a specific trait within a population"	Editorial suggestion noted and revision made.

Western Michigan University	43	22-23	Replacement drives have the goal of keeping the target population at the same levels but changing their characteristics so that they are no longer harmful, such as An. gambiae that can no longer serve as Plasmodium hosts. Thus these two different types of drive do not have this goal in common.	Comment noted and Revision made.
Outreach Network for Gene Drive Research	43	22-23	A "replacement drive" would not have the "ultimate goal" of "eradication of an invasive species or pest", but rather to modify it so that it would no longer present a threat.	Comment noted and Revision made.
Western Michigan University	43	23	For example, risk assessment should consider the possibility that...	Comment noted.
Imperial College London	43	24	It would be more precise to state "suppression" or "reduction" drive as stated in line 15.	Editorial suggestion noted and revision made.
Global Industry Coalition	43	24	**Insert** "*sexually compatible*" before "*species*"	Editorial suggestion noted and revision made.
Imperial College London	43	24-26	That distinction is not correct. A replacement drive could affect non-target species e.g. via hybridisation. Likewise, a suppression drive could potentially alter the target species in an unintended manner (e.g. through an off-target effect that makes mosquitoes more resistant to insecticides, if this is coupled with low effectiveness of the suppression this could pose a potential harm).	Comment noted and text revised.
Global Industry Coalition	43	27	Regarding the term "*synthetic biology organism containing an engineered gene drive*" - even within the CBD, this category of organisms is termed "living modified organisms containing engineered gene drives". Recommend that the authors should maintain this terminology.	Comment noted.
Global Industry Coalition	43	29	**Delete** "*synthetic*"	Editorial suggestion noted and revision made.
Imperial College London	43	33	This statement needs a reference. Further it is stated that resistance is important (?). It is rather an important concern.	Editorial suggestion noted and revision made.

Imperial College London	43	36	Resistances to target sites are not a phenomena (as is known for insecticides). Add reference.	Editorial suggestion noted and revision made.
IWF	43	37	The case studies or examples of any live research/project can be provided to concretely backup the argument.	Editorial suggestion noted.
Imperial College London	43	40	Please add a reference.	Editorial suggestion noted and revision made.
Western Michigan University	43	43-45	Research to overcome resistance should be mentioned as well.	Comment noted and Revision made.
Global Industry Coalition	43	43-45	Research to overcome resistance should also be mentioned.	Comment noted and Revision made.
Imperial College London	43	44-45	“It is rather uncertain how rapidly it spreads” What does this sentence imply? This does not constitute a potential harm.	Comment noted.
CDTBE-UK	43	45	This article by "Critical Scientists Switzerland" has been cited several times. The group is openly against the use of genome editing, GMOs and gene drives for sustainable development (see: https://criticalscientists.ch/images/css/Gene_Editing/Press-release-ENSSER-and-CSS-for-Leopoldina-counter-report_26Apr2021.pdf). The cited report also shows very clear bias against the use of gene drives, and provides no counter arguments for their beneficial application. When this document is cited in this report, it only supports the idea that there is "uncertainty" about their effects and that "further investigation is needed", whilst ignoring that these investigations are always ongoing by multiple parties. We conclude that they are not an appropriate source for this type of report.	See Scope & Methods section
Global Industry Coalition	43, 44	46-49, 01-10	This paragraph needs better placing into context. The concept of controlling/removing or introducing new/different species is not new or unique to synthetic biology. There are precedents for comparison, e.g. other LMOs and other disease vector/pest control strategies. In discussing the potential risks, they should not be considered in isolation (which exaggerates them) but in comparison to other tools that are used for addressing the	Comment noted.

			problem. It should also be noted that where there are potential significant public health benefits, morally and ethically this could necessitate consideration (and weighing) of both the potential benefits and risks. It is odd that this document stresses a range of factors as important in decision making elsewhere (e.g. p18, lines 8-9; section 5) but this section is narrowly confined to environmental risks.	
Global Industry Coalition	43	47-48	The term "ecosystem services" and the examples provided relate to humans, not to non-target organisms.	Comment noted and Revision made.
Outreach Network for Gene Drive Research	44	02-03	A population replacement drive would not necessarily lead to lower numbers of a target species.	Comment noted and Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	44	02-04	This is a theoretical assumption. The synthetic gene drive could, depending on the design, have negative unintended impacts on the target population leading to population crash or even loss of species.	Revision made.
Imperial College London	44	02-10	This does not consider the potential application of population suppression gene drives to alien species. Also, again the potential reduction in vector numbers is not unique for population suppression gene drives. This has been achieved through other vector control interventions (e.g. insecticides) as well.	Revision made.
Western Michigan University	44	03	Lower numbers are not the expected result of replacement drives.	Revision made.
Imperial College London	44	03	Lower numbers are not expected for mosquito replacement strategies.	Revision made.
Global Industry Coalition	44	03	Please note that lower numbers are not the expected result of replacement drives.	Revision made.
Outreach Network for Gene Drive Research	44	16-18	Current research does not support the assertion that gene drives are “likely to be highly invasive”. Invasiveness of specific constructs and applications will be determined by their particular characteristics, and many applications will not be self-sustaining.	Revision made.

Global Industry Coalition	44	16-18	**Revise** for factualness. The cited authors are not gene drive developers.	Editorial suggestion noted and revision made.
Imperial College London	44	16-20	As mentioned in the sentence about variation persistence before, the level of invasiveness depends on the construct and application and cannot be generalised for all gene drives.	Comment noted and Revision made.
Western Michigan University	44	17	Likelihood of invasiveness is a consequence of the design of the drive. Therefore, this is not a statement that can be made generally for gene drives, despite the opinions expressed in the sources cited. Some gene drives will be designed to not be self-sustaining.	Comment noted and Revision made.
Global Industry Coalition	44	17	**Insert** "*certain*" before "*gene drive*". The likelihood of invasiveness is a consequence of the design of the drive. Therefore, this statement cannot be made in general for gene drives as a whole.	Editorial suggestion noted and revision made.
Western Michigan University	44	19	However, spread would be limited by geographic distribution of target species, since the presence of the species is required for the gene drive construct to spread.	Comment noted and text revised.
Global Industry Coalition	44	20-24	This sentence presents (another) generalisation of risk and has a questionable rationale. Elsewhere in the report the authors highlight case-by-case assessment. As for other LMOs, the risks would be assessed prior to introduction with risk management measures introduced as necessary.	Comment noted and text revised.
Imperial College London	44	21	Replace "can" with "could" as that is speculative	Comment noted.
CDTBE-UK	44	22	There are strategies in production for self-limiting gene drives that have good confinement (https://doi.org/10.1038/s41467-020-14960-3)	Comment noted and text revised.
Imperial College London	44	22	Not all gene drive will affect food security.	Comment noted and text revised.
Imperial College London	44	23	Mitigate harm, implies that by default there is a harm to humans or the environment from using gene drives	Comment noted and text revised.

Global Industry Coalition	44	25	**Revise** for factualness. Multiple examples used by the authors in section 4.2 are not related to synthetic biology and should be deleted. Just because a developer is using Cripsr/cas, or any other current biotechnology tools does not make the product a synthetic biology product.	See scope and methods.
EBRC	44	Section 4.2	Recommend to mention impact of synthetic biology on food/feed processing, waste prevention,..(value-chain perspective)	Comment noted.
ISF	44/45	26 (pg 44)-28 (pg 45)	Section 4.2 list multiple examples of genome edited crop plants that are not the result of synthetic biology and should be deleted (for example once more canola plants with simple point mutation etc.).	See scope and methods.
Global Industry Coalition	44	30-31	**Delete** "*and that provide alternative weed control (e.g. Cibus' oilseed rape resistant to CLEARFIELD® herbicides*" or provide a reference to back the claim that this is an application of synthetic biology.	Editorial suggestion noted and revision made.
Western Michigan University	44	31	Many regulatory regimes would not regulate these as GMOs/LMOs. In fact, it is questionable whether these should be cited as examples of synthetic biology altogether.	See scope and methods
JCVI	44	35-40	The most comprehensive review of conventional GMO crops is "Genetically Engineered Crops: Experiences and Prospects", NASEM, 2016. At minimum, it needs to be included as a reference. A paragraph or two on its conclusions would be a very useful addition.	Comment noted and Revision made.
CDTBE-UK	44	38	These last two consequences are a result of choices not directly related to the use of this technology.	Comment noted.
PRRI	44	41-45	Genome editing techniques and tools may be the same but used in different ways.	Comment noted.
Global Industry Coalition	44, 45	41-48, 01-19	Genome edited plants are not the outcome of applications of synthetic biology and therefore the examples listed are not relevant and should be	See scope and methods.

			deleted (page 44, lines 47-48; page 45, lines 1-4). Further, on the topic of off-target mutations, as we have already pointed out, the European Food Safety Authority (EFSA) concluded that off-target mutations are likely to be fewer in edited organisms that in conventionally bred organisms. They also concluded that genome editing techniques that modify the DNA of plants do not pose higher of different hazards than conventional breeding or techniques that introduce new DNA into a plant. Revise for completeness: We suggest reviewing and referring to a broader sample of the scientific literature on this topic in the paragraph on page 44, lines 41-46. Delete entirely the paragraph on page 45, lines 5-19, it is not relevant to synthetic biology.	
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	45	05-06	This is not very precise, as the depth of intervention is clearly increased with genome editing. Off target effects are not considered to be independent of the target sequence in all cases for genome editing. That means that even though a lower number of off-targets might occur, those could accumulate in sequences related to the target sequence, which could e.g. influence multiple genes belonging to the same gene family. The comparison of genome editing and conventional plant breeding for risk assessment is not appropriate, as the number of unintended changes cannot be a proxy for risks that might be associated (Eckerstorfer et al. 2019).	Comment noted and Revision made.
Imperial College London	45	06-07	Comparing off-targets from conventional breeding to modern breeding technologies actually shows that off-targets are much lower in newer technologies. Singer, Stacy & Laurie, John & Bilichak, Andriy & Kumar, Santosh & Singh, Jaswinder. (2021). Genetic Variation and Unintended Risk in the Context of Old and New Breeding Techniques. Critical Reviews in Plant Sciences. 40. 1-41. 10.1080/07352689.2021.1883826.	Comment noted and Revision made.
CDTBE-UK	45	06	Nice point, mutagenizing chemicals and radiation have been long in use and generate unpredictable mutations that are then selected for through breeding. These have not been nearly as strictly contained as GMO crops, and these "non-natural" mutations do not accumulate and are removed by pressure.	Comment noted.

			There is no reason that achieving the same phenotype by minimal changes through directed mutagenesis will not follow the same trend.	
EBRC	45	12	There is no scientific basis for this statement. Recommend correction.	Comment noted.
EBRC	45	21	Zhao and Wolt 2017 is mis-cited. The review only acknowledges that there are "concerns" but largely makes the case that technology per se does not increase the likelihood of a deleterious event that goes on to pose a risk to humans, animals or the environment.	Comment noted and Revision made.
EBRC	45	22	The discussion of the potential for crop domestication to introduce toxic metabolites into the food supply or environment has no bearing on the role of synthetic biology in agriculture. Recommend clarification or removal.	Comment noted and Revision made.
CDTBE-UK	45	27	Again, both cited groups are outwardly anti-GMO relating to agriculture. The report from CBAN makes reference to a contentious study on p53-associated arrest in human cells in the presence of Cas9, the implication being that edited cells may be more likely to become malignant. Acknowledging that this process is not at all comparable in plants, the worst case scenario of this would be a damaged, non-viable crop, which can easily be replaced by another with an optimised edit.	Comment noted and Revision made.
PRRI	45	15-28	The possible off-target alterations of genome editing are mentioned but it is not discussed the possibilities to identify them as well as how genome edited crops are regulated when off target effects are present. In addition off target effects are not exclusive to synthetic biology they also occur in conventional breeding.	Comment noted.
Global Industry Coalition	45	20-21	**Revise** for factualness. "*Concerns have also been raised surrounding the generation of plant allergens, toxins and anti-nutrients, which may pose a risk to human and animal health*" Please provide context to this statement, and indicate that this is a standard consideration in the case by case risk assessment of LMOs.	Comment noted and Revision made.

Global Industry Coalition	45	27 (and elsewhere)	The authors must clearly identify the scientific merit of the publications they refer to. It is highly misleading to compare genuine scientific information that provided by interest group materials. If used, these need to be acknowledged.	See Scope & Methods section.
EBRC	45	Section 4.3	Recommend to mention impact synthetic biology on industrial enzymes sector with significant impact on sustainability (lowT, low water washing,.)	Comment noted.
PRRI	45	30	to help tackle climate change **challenges** (it seems a word like the word "challenges" is missing).	Comment noted and Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	46	10	"service provided": CBD is committed to protect biodiversity as a whole. The concept of ecosystem services is inappropriate in this regard.	Comment noted.
EBRC	46	25-28	Apart from new, non-food feedstocks, synthetic biology has already had a significant impact on fuels and chemicals applications still relying on sugar (1, 1.5 G generation of feedstocks), enabling the industry to reduce carbon footprint and to transition to non-food feedstocks.	Comment noted.
CDTBE-UK	46	37	The preceding sentence needs much more weight - many agree that despite the potential risks, using SynBio technologies in this space would be a net benefit to the ecosystem. This is a fairly conclusive justification for these commenters. The ETC suggesting that "considerable uncertainty remains" is not close to being a good justification to not pursue this; uncertainty exists in every scenario where an outcome cannot be definitively predicted, however much work is being done to reduce this uncertainty, and what is much less uncertain is that our current actions globally are wholly insufficient in tackling the climate crisis.	Comment noted.
PRRI	46	37	There is always some uncertainty – this is not something only related to synthetic biology. The word "considerable" is vague means different things to different people. There are efforts to minimize uncertainty and RA&M on a case by case is normal.	Comment noted and Revision made.

ETC Group	46	37	The paper notes considerable uncertainty, but does not explain the seriousness of the threat in a reasonable worst case scenario - i.e. that the use of Synbio could destabilise whole ecosystems, and potentially the global meteorological systems, with potentially devastating results.	Comment noted.
African Centre for Biodiversity	46	37	The paper cited goes beyond noting considerable uncertainty, but also raises the seriousness of the threat in a reasonable worse-case scenario - i.e. that the use of synthetic biology could destabilise whole ecosystems, and potentially the global meteorological systems, with potentially devastating results. This sentence should reflect the paper adequately.	Comment noted.
PRRI	46	40-43	RA&M measures as appropriate are considered to prevent adverse effects	Comment noted and Revision made.
CDTBE-UK	46	41	Biocontainment strategies (synthetic auxotrophies ect.) are being developed to address this specific issue.	Comment noted.
CDTBE-UK	46	47	The statements made in the rest of this section are important to understanding the potential of SynBio for applications in climate change. It's a very short summary, and the benefits of these techs do not receive an appropriate weighting in the form presented here.	Comment noted.
EBRC	47	05-11	Recommend to extend this section to cover the many synthetic biology developments in cellular fermentation to produce animal, fish,.. proteins., in line with 3.3.1 p36.	Comment noted and Revision made.
CDTBE-UK	47	23	A comparison could be made to synthetic diamonds as an example of reducing dependency on an exploitative illegal market, and as such increasing the quality of life of individuals associated with harvesting the commodity.	Comment noted.
Global Industry Coalition	47	25	**Missing reference**. "*disrupt in situ conservation projects*" Please back this statement with a research article demonstrating such potential.	Revision made.

CDTBE-UK	47	33	As with many technologies, it is predicted that many jobs will be lost in turn. However, new jobs will also become available, especially if SynBio technologies can be democratised and made available to all areas for production of essential goods.	Comment noted. Economic concerns are addressed later in Section 5.2.
IWF	47	33	More dataset will be need to make a conclusive argument.	Comment noted.
Global Industry Coalition	47	36	**Delete** "*seems to*" and **add** "s" to "*support*"	Editorial suggestion noted and revision made.
Global Industry Coalition	47	37-38	Please add a note on the difference between vanilla (the natural product) and vanillin (the synthesised compound). Vanillin and vanilla compete in different markets (see e.g. https://www.nature.com/articles/nbt.3191).	Comment noted.
Global Industry Coalition	47	40	**Insert** "*compared to the vanillin molecule*" after "*profile*"	Editorial suggestion noted.
Global Industry Coalition	47	40	**Replace** *"As a consequence, UNCTAD expect that the naturally sourced product"* with, "*According to the report, naturally sourced vanilla*."	Editorial suggestion noted.
EBRC	47	Section 5	Recommend to use same classification (unmanaged-(semi) managed-contained for section 5 concerns-chapters to enable better category related information and recommendations	Editorial suggestion noted.
Global Industry Coalition	48	01	Insert "voluntary" before "guidance". Insert "in the context of reaching a decision on LMO import per Article 26 of the Cartagena Protocol" after "concerns". Replace "has recently emerged" with "is in development and yet to be considered or adopted by CP Parties"	Editorial suggestions noted and revisions made.
PRRI	48-50	5.1.1 and 5.1.2	Adequate Public and Indigenous engagement needs and an adequate understanding of the highly technical developments. This part misses the importance of the latter.	Revision made.

Western Michigan University	48	08	This section seems quite judgmental, emphasizing the need to consult society as a whole rather than those elements of society that are most likely to be affected by the technology. This is counter to the common thinking that the opinions of those who will be most impacted should be prioritized.	Comment noted.
IWF	48	08	More dataset will be need to make a conclusive argument.	Comment noted.
Global Industry Coalition	48	08	**Replace** "*concerns*" with "*considerations*"	Editorial suggestion noted.
Global Industry Coalition	48	08-27	**Revise** for factualness. The whole first paragraph in section 5.1.1 is highly biased. Some specific edits are suggested below, however further revision by the authors is recommended.	Comment noted.
Global Industry Coalition	48	13	**Insert** "*science based*" before "*risk assessment*" **Insert** "*conducted in accordance with the principles set out in the Cartagena Protocol.*" after "*risk assessment*"	Comment noted.
Global Industry Coalition	48	17	**Replace** "*must be included in the process of judging*" with "*influence judgement of*" Regarding the sentences in lines 14-18 – this process is not new or specific to synthetic biology, and does not need to be "fixed" to accommodate synthetic biology. It should always be the case that decisions are determined by a robust assessment of the potential risks of the product, with that assessment and decision-making process shaped by policy aims that take into consideration the needs of society. These processes are determined at the national government level according to national priorities and circumstances. It is not the scope of this document (or CBD) to instruct on policy making.	Comment noted.
Global Industry Coalition	48	18-20	**Revise** for factualness. What types of applications are being referred to here? Is this mixing medical applications (not in scope) with those intended for environmental release? For the agricultural examples presented in this document, there are ongoing discussions about the appropriate level of regulation within existing biotech frameworks, not about "responsible application".	Comment noted and Revision made.

Max Planck Institute for Terrestrial Microbiology	48	19 ff	Potential negative impacts are attributed to the technology that are not technology-specific, but rather broader social practices for example over-farming/aggressive monopoly business models.	Comment noted.
Global Industry Coalition	48	21	**Revise** for factualness. " *which are likely to be the first to feel any potential impact*" What evidence can be provided to support the claim? If the statement reflects views of specific organisations, this should be acknowledged as an opinion, not a fact.	Comment noted.
Global Industry Coalition	48	22	**Replace** "*Thus, the acceptability of any risk is a social construct, as are the*" with "*The level of risk that is acceptable in a society will depend on many factors...*"	Editorial suggestion noted.
Imperial College London	48	22-24	This consultation should include views on risks as well as benefits from these communities	Revision made.
Western Michigan University	48	23	This document should also consider adding in this section a comment about the ethical obligation not to disseminate misinformation in the context of "informed consultations"	Comment noted.
Global Industry Coalition	48	23	**Revise** "*…should be informed through consultation with a broad set of stakeholders*". This seems to be prescribing how national governments should develop policy? We note again, that national decision-making is not the scope of this document or the CBD.	Comment noted.
IWF	48	24	The local communities should also be in loop.	Comment noted.
Western Michigan University	48	24-25	These stakeholder consultations should consider local populations' view of benefits as well as risks, consistent with what is said previously in these comments (see comments to p.12, lines 34-38; and p. 41, line 25).	Revision made.
Global Industry Coalition	48	28	**Missing reference**. "*technologies that affect the global commons*". What technologies are you having in mind here? Also, please add an explanation of	Revision made.

			what "global commons" is to make it easier for the reader to understand what is discussed in this paragraph.	
Global Industry Coalition	48	29	**Revise** for factualness. "….*should be published in advance*". This is what happens - normal scientific practice is to publish research concepts, and results of early stage research.	Comment noted and Revision made.
Imperial College London	48	29-34	Applications should be published in advance of construction of any synthetic biology technology? Is that requirement and generalisation proportional to other technologies? These technologies are developed in containment laboratories and are not released without permission.	Comment noted.
Global Industry Coalition	48	31	**Revise** for factualness. "…*conventions*" is this referring to adaptation of Treaties?	Comment noted and Revision made.
Global Industry Coalition	48	38	How are "new breeding techniques" as a whole relevant to synthetic biology?	Comment noted.
Imperial College London	48	39	Should there not be a priority on those most affected by the specific application. How different are protection goals between different communities?	Comment noted.
Imperial College London	48	44	See comment above. Not everyone will be affected by these applications. Therefore, the view of those most affected by the application should be prioritised.	Comment noted.
Imperial College London	48	46	The extend to which that harm be acceptable and consideration of the benefits the technology might provide.	Comment noted.
EBRC	48	5.1.1	Text describes a conceptual, predictive process, difficult to reconcile with typical disruptive paths of science and innovations. See remark on p11-12 on message 10: how to realize in practice?	Comment noted.

Western Michigan University	49	01	This statement further supports a risk and benefits consideration when assessing the impacts of the technologies mentioned in the document and subsequently deciding to approve or deny it.	Comment noted.
Imperial College London	49	01	Yes, this would involve rather a risk-benefit analysis then just a risk assessment	Comment noted.
Max Planck Institute for Terrestrial Microbiology	50	16 ff	"*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*". A big concern in this statement is the lack of a clear commitment to scientific theory and fact-based argumentation as guiding principle for decision-making. We agree that there is a need for scientific bodies to continuously engage in dialogue with the public and to increase the quality of that dialogue, as well as a need to promote transparent information sharing. However, there also needs to be an in-principle agreement on the possibility of attaining an objective definition of risk. We would strongly caution against bringing broader policy and societal issues into regulatory issues related to synthetic biology and instead strongly favour an evidence-based approach, including evidence-based decision-making guided by the scientific community on a case-by-case basis to avoid violating biodiversity and sustainability goals. While it is important to consider societal and ethical concerns relating to synthetic biology research and applications, we find it also important that potential and realized benefits to society and environment are widely publicized for an informed discussion in the public. Considering the polarized and emotionalized discussion on the generation and release of genetically modified organisms in the past, we deem it essential to fairly weigh risks and benefits based on a scientifically informed discussion to prevent the ban of technologies that hold significant promise to solve societal and ecological problems. We also would like to stress that any discussion on technologies needs to incorporate considerations of potential alternatives and their benefits and risks (e.g., the use of pesticides versus specifically designed biocontrol	Comment noted.

			agents). We would also like to highlight that many of the risks discussed in the text in general are not related to the specific technology of "synthetic biology", but rather to broader social practices, such as aggressive monopoly business models.	
PRRI	50	31-32	There are many different types of Gene drives been conceived as well as safety strategies, they do not have to always carry potential risk of irreversibility once released in the wild.	Comment noted.
ETC Group	50	33	Describes engagement processes initiated by proponents of Synbio, but ignores critiques of such engagement processes and the problem of ethics dumping in the Global South (Bassey-Orovwuje et al. 2019). Bassey-Orovwuje, M., Thomas, J. & Wakeford, T. Exterminator Genes: The Right to Say No to Ethics Dumping. Development 62, 121–127 (2019). https://doi.org/10.1057/s41301-019-00214-3	Comment noted and Revision made.
African Centre for Biodiversity	50	33	This section ignores critiques of engagement processes and the problem of ethics dumping in the Global South (Bassey-Orovwuje et al. 2019). Bassey-Orovwuje, M., Thomas, J. & Wakeford, T. Exterminator Genes: The Right to Say No to Ethics Dumping. Development 62, 121–127 (2019). https://doi.org/10.1057/s41301-019-00214-3	Comment noted and Revision made.
Third World Network	50	35-43	A clear distinction should be made between the engagement strategies from developers or proponents of a technology, such as highlighted in this section (e.g. Target Malaria) and genuine processes that aim to obtain the free, prior and informed consent (FPIC) of potentially affected communities. In the former, there could be potential conflicts of interests, and questions can be asked as to whether the consent that is sought is freely given without pressure or manipulation, and whether the information that is provided is unbiased and explains the risks adequately.	Comment noted and Revision made.
ETC Group	50	35-43	A clear distinction should be made between the engagement strategies from developers or proponents of a technology, such as highlighted in this section (e.g. Target Malaria) and genuine processes that aim to obtain the free, prior	Comment noted and Revision made.

			and informed consent (FPIC) of potentially affected communities. In the former, there could be potential conflicts of interests, and questions can be asked as to whether the consent that is sought is freely given without pressure or manipulation, and whether the information that is provided is unbiased and explains the risks adequately.	
African Centre for Biodiversity	50	35-43	As stated in general comments, a clear distinction should be made between the engagement strategies from developers or proponents of a technology, such as highlighted in this section (e.g. Target Malaria) and genuine processes that aim to obtain the free, prior and informed consent (FPIC) of potentially affected communities, the issues of potential conflict of interests, where consent is given without pressure or manipulation, and where information that is provided is unbiased and explains the risks adequately.	Comment noted and Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	50	40	It would lead to an " engineered living modified gene drive mosquito"	Comment noted.
Global Industry Coalition	51	01	**Replace** "*concerns*" with "*considerations*"	Editorial suggestion noted.
Global Industry Coalition	51	06	**Replace** "*import and export*" with "*transboundary movement*"	Editorial suggestion noted and revision made.
Global Industry Coalition	51	26	**Replace** "*for wild caught species*" with "*for products from wild species*"	Editorial suggestion noted and revision made.
Global Industry Coalition	51	27-29	Please add examples to the sentence "*Further… synthetic chemistry*".	Editorial suggestion noted and revision made.
Global Industry Coalition	51	35	**Delete** "*rather than artificial*" The contrast between "natural" and "artificial" is misleading (and itself artificial)	Editorial suggestion noted.

Global Industry Coalition	51	36	**Replace** "*displacement*" with "*substitution*"	Editorial suggestion noted and revision made.
Global Industry Coalition	51	37	**Delete** "*negative*"	Editorial suggestion noted and revision made.
EBRC	51	42-46	Important finding and statement with impact for 48 section 5.1.1 remark above	Comment noted.
Global Industry Coalition	51	48	**Replace** "*using synthetic biology techniques via fermentation in yeast*" with "*by yeast fermentation*"	Editorial suggestion noted and revision made.
Global Industry Coalition	52	02	**Replace** "*synthetic biology vanillin*" with "*vanillin from yeast fermentation*"	Editorial suggestion noted.
Global Industry Coalition	52	04-07	Please indicate what "potential adverse effects" could arise.	Comment noted and text added.
Western Michigan University	52	05-06	The WHO (2021) perspective should be included here, as in this quote: "It is important to avoid processes that privilege some communities over others, leading to procedural injustice and inequity. The key message for researchers is that efforts should be made to ensure that communities, stakeholders and publics are appropriately engaged, and that host communities for GMM release are given the opportunity to provide legitimate authorization for the release.	Comment noted. Revision made.
Global Industry Coalition	52	35	**Replace** "*concerns*" with "*considerations*"	Editorial suggestion noted.
ETC Group	52	44	This is an inadequate discussion of the ethical and epistemological arguments about gene drives in the context of Indigenous people's autonomy, cosmovisions and knowledge systems. The economic paradigm of ecosystems services (Line 49) is just one methodology that people have devised to value biodiversity and is not considered appropriate by a wide range of Indigenous peoples and local communities (Goldtooth 2016). Goldtooth, T (2016). Judge's Statement. Paris International Rights of Nature Tribunal. https://www.therightsofnature.org/paris-financialization-of-nature/	Comment noted and Revision made.

African Centre for Biodiversity	52-53	44-5	The discussion on ethical concerns is incredibly limited, reflecting the "attitudes" rather than the real interests and valuing of nature beyond the limited economic valuing outlined. The economic paradigm of ecosystems services (Line 49) is just one methodology that people have devised to value biodiversity and is not considered appropriate by a wide range of Indigenous peoples and local communities, and fails to fully understand the impacts on indigenous peoples' and local communities, including farming communities' autonomy, knowledge systems, and livelihoods (Goldtooth 2016). Goldtooth, T (2016). Judge's Statement. Paris International Rights of Nature Tribunal. https://www.therightsofnature.org/paris-financialization-of-nature/	Comment noted and Revision made.
CDTBE-UK	53	08	Biological patents have been an issue within other fields of biology, and were raised long before SynBio as a field was mature. Current ruling is that naturally occurring DNA sequences are not possible to patent, while synthetic material or that which has been isolated or processed from a biological source (recombinant insulin used in large scale production being a high profile example). SynBio could exacerbate concerns on IP, but there are rulings in place currently that govern this, and that can be further built upon.	Comment noted.
PRRI	53	08-11	The patent system if adequate helps to stimulate investment in research, development and innovations. It is not necessarily negative. In addition, while synthetic biology is likely to generate patentable products and processes there is also considerable emphasis on the open source model, particularly in the development of standards, components and platforms for research. The BioBrick Public Agreement provides researchers a means to licence use of components on open-source principles.	Comment noted.
Global Industry Coalition	53	15	**Revise** for factualness. "…*concentrate power with a few corporations*". Statements such as this should be supported by evidence instead of by references to work by interest groups or NGO claims. Fact: CRISPR patents are not owned by corporations.	Comment noted.

Global Industry Coalition	53	33	**Revise** for factualness. "… *novel mode of action*". What is this referring to? Genetic engineering is not "novel".	Comment noted.
Imperial College London	53	35-40	Again, this concern is not specific to synthetic biology technologies. Common breeding techniques are not natural.	Comment noted.
CDTBE-UK	53	40	For instance; if a species were heading towards extinction, even if man-related issues were not related to the cause, putting mechanisms in place to protect the species could be seen as intervening in a natural process. The effects of man-made climate change and destruction of natural habitats to serve our purpose has already had irrevocable effects on the "naturalness" of the planet, and the use of biotechnology will in most cases not match that level of disruption.	Comment noted.
CDTBE-UK	53	46	Agriculture, and the enrichment of certain phenotypes through selective breeding, also involves a disruption to natural homeostasis to serve our needs. There are many instances in nature of species moulding their environment so that they can thrive, this is nothing new, albeit on a larger scale.	Comment noted.
CDTBE-UK	53	47	Very true; this could be explained in more detail, to give adequate weight to the side of the argument that suggests	Comment noted.
CDTBE-UK	53	48	This sentence doesn't make sense, may need to re-write this.	Comment noted and Revision made.
IWF	53	48	The sentence need be re-written to be clearer	Comment noted and Revision made.
Imperial College London	53	48-50	The messaging of that sentence is not clear. It is not by default that this technology causes harm.	Comment noted and Revision made.
Brazilian Bar Association	54	01-12	Moral, ethical and legal debates have influenced the development of animal rights in Brazil, resulting in penalties for mistreatment in the administrative and criminal spheres, as established in Law 9605/1998. Moreover, Law 11.105/2005 includes provisions on animal protection in relation to GMOs.	Comment noted.

Global Industry Coalition	54	06	**Insert** "*the human values of*" before "*self-determination*"	Editorial suggestion noted Revision made.
CDTBE-UK	54	08	This is entirely speculation, and a conversation rooted in the use of animals in science and research. SynBio applications on cell-free systems, minimal cells and differentiated tissues and organoids, for just a few examples, are being developed in part as a means to reduce the need for animals in testing, and would therefore be beneficial in this light. This is not mentioned here, and ought to be.	Editorial suggestion noted Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	54	13-25	It should be noted here, that synbio applications for nature conservation might not achieve the intended goal, as they would interact in complex ecosystems, and also that those applications do not correct the initial problem but instead aim to mitigate the consequences (e.g. of climate change).	Comment noted and Revision made.
ZKBS	54	18-20	Concerning the sentences: "A recent example is the ongoing conversation about the responsible application of CRISPR that is taking place at both national and international levels concerning the limitations of current global governance structures to safeguard its use. Largely missing from this conversation however, is attention to local communities in decision-making which are likely to be the first to feel any potential impact from these applications (Kofler et al., 2018)" à CRISPR itself is a technique that can be applied for a variety of purposes. Only one of its applications is the creation of organisms containing an engineered gene drive that may affect local communities. The text should be specified accordingly.	Comment noted and Revision made.
EBRC	54	20-24	Very important statement, recommend for it to have a more prominent position in document	Comment noted and Revision made.
CDTBE-UK	54	21	Equally, concerns many may have about "Trojan horses" relating to misuse of SynBio tech also need to be grounded in evidence. Overall, this section puts very little focus, and minimal citations, on the side of the conservationists who see the potential benefits of these technologies.	Comment noted.
Global Industry Coalition	54	26	**Replace** "*concerns arising from dual use*" to "*Considerations related to dual use organisms*"	Editorial suggestion noted.

Global Industry Coalition	54	27	Please **provide a definition** of "dual-use" at the beginning of this paragraph.	Comment noted and Revision made..
JCVI	54	33-37	As a co-author of Garfinkel et al. 2007, I was very surprised to see this extremely speculative statement ascribed to our study. We did not suggest this. The Mukunda paper includes this particular speculation among a long list of possible speculations for the future, one or some of which might happen in more than 10 years. I suggest that these lines be deleted.	Comment noted and Revision made.
EBRC	54	35-36	The Mukunda 2009 paper is quoted here without any attempt at contextualizing the difficulty with 'biological weapons customised to attack specific groups' – namely that test and evaluation of such weapons is prohibitively complex, in the sense that narrow targeting requires more a complicated biological system, which in turn increases the need for testing, but given the narrowness of the targeting for the weapon, finding ways to reliably test gets more and more difficult if not impossible. It would be useful for this summary to mention this (massive) limitation to such weapons – the current text risks creating unfounded panic at the likelihood of genetically targeted weapons.	Comment noted and Revision made.
CDTBE-UK	54	46	This is critical; these technologies exist and mechanisms are in place to monitor, legislate and tackle their misuse. Similar indictments occur within the information technology space, and much attention is focused on counter-cyber activities by governments. Further research is needed to understand how to deal with these potential problems, as it is definitely possible that dual use will occur even at the technology level we have today. The only way to counter this is to further understand and evolve the technology and find it's critical potential and limitations.	Comment noted and Revision made.
WHO	54		Definitions of BW and CW could perhaps be included (from the BWC and CWC). A current key focus on non-standard CW agents are aerosolized central nervous acting chemicals such as fentanyl derivatives. Has any individual or group performed sophisticated scientific research and lab work?	Comment noted.

			It could be useful to consider WHO's R&D blueprint and disease X in this context.	
JCVI	54, 55	48-50, 1-14	This is the second time the "insect allies" research program has been discussed in the report. Why is this much text devoted to what the report describes as speculations?	Comment noted.
CDTBE-UK	55	25	Key point, law enforcement will need to develop in step with the technologies, as changing the direction of public research or stopping it all together will likely not be sufficient in stopping individuals from pursuing their own dual use goals.	Comment noted and Revision made.
EBRC	55	26	The cited Koblentz paper does NOT state that 'no country regulates sales of synthetic DNA" – the relevant passage from the Koblentz paper states only that "no country requires the companies that sell synthetic DNA to prevent "questionable parties" from acquiring materials." The United States does regulate the sale of any synthetic DNA that can transfer pathogenicity from agents and toxins on the Select Agent list, c.f. https://www.selectagents.gov/regulations/interpretations/dna.htm. In addition, sequences from listed agents that can 'endow or enhance' pathogenicity require a license for export outside of the United States and 42 other countries in the Australia Group, see https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/participants.html and the section on "Genetic Elements and Genetically-modified Organisms" on https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/human_animal_pathogens.html	Comment noted. Revision made.
Global Industry Coalition	55	26	**Revise** for factualness. The statement "*no country regulates the sales of synthetic DNA*" is factually incorrect. Countries may not regulate DNA synthesis and sales under GMO regulations, however a number of health and safety regulation apply, as well as product safety and product quality regulations that also have provisions for consumer / user protection. Environmental liability regulations / legislation equally are fully applicable.	Comment noted and Revision made.

EBRC	55	32	IGSC members do not use “a relatively short list of biological toxins and select agent genomes” – doing so would lead to a high false positive hit rate given homology between pathogens and non-pathogens. Most IGSC members instead align to a very large reference database (often NCBI’s nr set of all non-redundant protein sequences) specifically because there is no single source of all regulated individual sequences. Screening systems instead align to a large set of sequences and then summarize findings of uniqueness to controlled pathogens for expert human review and final decision making.	Comment noted and Revision made.
EBRC	55	38-40	It is unclear what the phrase “cyber-hacking malicious code obfuscation” is intended to mean – nor is it clear what “use a malicious sequence” might mean. This sentence should be rewritten to be clear, concise and specific – suggest: “Depending upon screening implementation, some DNA sequence obfuscation techniques may permit unauthorized access to controlled DNA sequences.”	Editorial suggestion noted and Revision made.
CDTBE-UK	55	41	This is a case where further research is beneficial; better prediction algorithms that could be employed by these companies to recognise dangerous sequences.	Comment noted.
IWF	55	41	More dataset will be need to make a conclusive argument.	Comment noted.
EBRC	55	41	The Puzis et al paper was specific only to conotoxins, extremely short peptides which, while subject to regulatory control, are also encoded for by DNA that is less than the 200 bp threshold under 2010 U.S. government guidance to DNA synthesis providers. The Puzis paper was a valuable contribution but it is recommended to contextualize what is meant here by ‘toxic peptide’ in that the paper did not demonstrate a generalizable exploint in screening systems.	Comment noted.
CDTBE-UK	55	43	Having the knowledge to produce these threats is different from being able to accurately produce them functionally at scale. There is accessible information online on how to develop high explosive, chemical or small nuclear weapons.	Comment noted.

			However, non-state actors lack the materials and facilities to build them, and as such they may pose little threat in actuality.	
EBRC	56	02-03	This sentence rightly affirms that the difficulty of weaponization should not be underestimated, but then makes no statement as to the level of that difficulty – this would leave less-technical audiences unaware of the important difficulties that keep weaponization of biology difficult. Recommend adding a statement here to reinforce awareness that synthetic biology does not make it any easier to package, dry-down, mill, disseminate or persist a biological weapon.	Comment noted.
WHO	56	03	Explosively disseminated and aerosol dispersal are perhaps improved phrasing.	Editorial suggestion noted and Revision made.
Global Industry Coalition	56	36	**Replace** "*concerns*" with "*considerations*"	Comment noted.
Global Industry Coalition	56	36-44	The section is supposed to address "*general biosafety concerns related to the accidental or intentional release of organisms resulting from synthetic biology*", and it further intends to address "*the suitability of existing risk assessment methodologies as well as potential management strategies*". Yet, the three specific examples that have been selected (engineered gene drives, gene editing and RNAi sprays) add little value in clarifying what are these specific challenges. Specific comments addressing problematic elements in the text in this chapter are provided in the comments below.	Comment noted.
Global Industry Coalition	56	38	**Replace** "*concerns*" with "*considerations*"	Comment noted.
Imperial College London	56	39-40	They are also product specific.	Comment noted and text added.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	56	42-44	"The section does not intend to be a comprehensive list or guide of issues to be considered under any specific assessment, as every potential analysis will have to be done on a case-by-case basis and in accordance with national and international regulations."	Editorial suggestion noted.

			As this sentence contains language from the Cartagena Protocol it should be amended by reminding of the precautionary approach, by including " and taking into account the precautionary approach" after "international regulations".	
Global Industry Coalition	56	47	**Replace** "*less*" with "*no, or little*"	Editorial suggestion noted Revision made.
EBRC	56	Section 6	Recommendation to use same classification (unmanaged-(semi) managed-contained for section 6 biosafety concerns-chapters to enable better category related information and recommendations	Editorial suggestion noted and Revision made.
Global Industry Coalition	57	02	**Replace** "*products*" with "*organisms*"	Editorial suggestion noted.
Global Industry Coalition	57	06	The reference is of questionable relevance – sources with regulatory expertise should be used.	See Scope & Methods
Global Industry Coalition	57	10	**Replace** "*This process will be influenced*" with "*While the risk assessment should be based on specific science-based hypotheses, the final decision will be influenced*"	Editorial suggestion noted.
JCVI	57	14-16	Such a sweeping generalization is far too broad to apply to all "synthetic biology applications" and as stated, highly misleading about challenges to regulation. In fact, the Duensing article cited as the source of the statement comes to the opposite conclusion in the abstract: "Since genome editing can lead to the development of plants that could also have come into existence naturally or by conventional breeding techniques, there are strong arguments that these cases should not be classified as genetically modified organisms (GMOs) and be regulated no differently from conventionally bred crops." The introductory paragraph to section 7 (Governance and Regulation) is a much more accurate statement	Comment noted and Revision made.
Global Industry Coalition	57	15	**Revise** for factualness. "… *novel risks and impacts, the high levels of uncertainty*".	Editorial suggestion noted. Revision made.

			Has this really happened yet? The regulators participating in the synthetic biology work under the CBD over recent years indicate that it has not.	
Global Industry Coalition	57	17	**Missing reference**. **Revise** for factualness. "*ever-increasing pace of development of these technologies*". Statements like this need to be supported by evidence - and it is not supported by the information in this document.	Revision made.
CDTBE-UK	57	20-21	It is critically important to stress that risk assessment is informed by the scientific data at all points, and that all stakeholders are sufficiently and correctly informed of the risks, the available mitigation strategies and control mechanisms in the engineered implementation. Proper stakeholder education of which failure modes are possible, which are impossible, and the likelihood of all on the risk spectrum, is of critical importance to prevent misunderstanding and fear of new technologies. Further, conversations with stakeholders must also discuss risk assessment of the solutions currently utilised. As an example, growing insecticide resistance in mosquito populations (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7477762/) presents a looming danger of critical failure for this method of malarial control, and a failure to discuss this side of the problem when weighing up alternative solutions such as gene drives (6.1.1.) is flawed at best, and dangerous at worst. For many important applications of emerging technologies, we must stress whether or not we can afford to maintain the status quo, whether we can afford to pass on these emerging solutions.	Comment noted. See Section 5
ETC Group	57	21	We strongly support the statement that the acceptability of risk is a social construct (i.e. an issue to be decided through legitimate political processes) and thus must involve a wide range of non-scientific criteria along with scientific parameters as one in the list of needed evaluation criteria, that can be debated as part of processes of participatory democracy. Indigenous and community farmers knowledge systems should be part of the risk assessment criteria, as well as their right to FPIC.	Comment noted.

African Centre for Biodiversity	57	21	We strongly support the statement that the acceptability of risk is a social construct (i.e. an issue to be decided through legitimate political processes) and thus must involve a wide range of non-scientific criteria along with scientific parameters as one in the list of needed evaluation criteria, that can be debated as part of processes of participatory democracy. Indigenous and community farmers knowledge systems should be part of the risk assessment criteria, as well as their right to FPIC.	Comment noted.
Global Industry Coalition	57	23-25	**Delete** last sentence**.** Repeating content in 5.1.1 - suggest removing it from this section.	Comment noted and text revised.
Global Industry Coalition	57	27-28	**Delete** "*what could go wrong and*"	Editorial suggestion noted.
Third World Network	57	27-30	This section could be strengthened to include the following reference (Heinemann et al, 2021) that refers to the increasing scale of human interventions as a result of emerging technologies (e.g. dsRNAs, gene drives, genome editing), which is now substantially increasing the likelihood of large-scale genetic (and other) environmental interventions. Scale of intervention can thus be considered as a risk in itself, and a major concern when considering the rapid development of synbio technologies for environmental release. As highlighted by Heinemann et al. (2021), mutations introduced by genome editing or other genetic technologies are not reliant on the processes of evolution, but instead can be driven by human activity, to ensure such mutations establish and spread in the environment. Heinemann, J. A., Paull, D. J., Walker, S., & Kurenbach, B. (2021). Differentiated impacts of human interventions on nature. Elementa: Science of the Anthropocene, 9(1), 00086. https://doi.org/10.1525/elementa.2021.00086	Editorial suggestion noted and Revision made.
ETC Group	57	27-30	This section could be strengthened to include the paper by Heinemann et al, (2021), which refers to the increasing scale of human interventions as a result of emerging technologies (e.g. dsRNAs, gene drives, genome editing), which is now becoming part of what could be considered genetic engineering of whole environments. The scale of such interventions can be considered to be	Editorial suggestion noted and Revision made.

			a risk in itself, and a major concern when considering the rapid development of synbio technologies for environmental release. As highlighted by Heinemann et al. (2021), mutations introduced by genome editing or other genetic technologies are not reliant on the processes of evolution, but instead can be driven by human attempts to ensure such mutations establish and spread in the environment. Heinemann, J. A., Paull, D. J., Walker, S., & Kurenbach, B. (2021). Differentiated impacts of human interventions on nature. Elementa: Science of the Anthropocene, 9(1), 00086. https://doi.org/10.1525/elementa.2021.00086	
African Centre for Biodiversity	57	27-30	This section could be strengthened to include the following reference (Heinemann et al, 2021) that refers to the increasing scale of human interventions as a result of emerging technologies (e.g. dsRNAs, gene drives, genome editing), which is now substantially increasing the likelihood of large-scale genetic (and other) environmental interventions, which can be considered as a risk in itself, and a major concern when considering the rapid development of synthetic biology technologies for environmental release. As highlighted by Heinemann et al. (2021), mutations introduced by genome editing or other genetic technologies are not reliant on the processes of evolution, but instead can be driven by human activity, to ensure such mutations establish and spread in the environment. Heinemann, J. A., Paull, D. J., Walker, S., & Kurenbach, B. (2021). Differentiated impacts of human interventions on nature. Elementa: Science of the Anthropocene, 9(1), 00086. https://doi.org/10.1525/elementa.2021.00086	Editorial suggestion noted and Revision made.
Global Industry Coalition	57	40	**Delete** "*the 'Points to Consider' in*"	Editorial suggestion noted and Revision made.
Global Industry Coalition	57	40-41	**Delete** *"of the Protocol"*	Editorial suggestion noted and Revision made.
Global Industry Coalition	57	41-42	**Delete** "*is a good summary of the types of information that are regularly considered during a risk assessment*" and **replace with** "*sets out the general*	Editorial suggestion noted and Revision made.

			principles of a science-based risk assessment, and general methodology including "points to consider"	
Global Industry Coalition	57	42-43	**Delete** "*and that may be extended/adapted to some applications resulting from synthetic biology*."	Editorial suggestion noted.
Global Industry Coalition	57	46	**Section 6.1.1** This section needs to mention that there are different types of drives with different potential scales of dispersal.	Comment noted. Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	57	48	The term "benefits" is inappropriate here and should be deleted, as this section is dedicated to biosafety. Relevant for the CBD is in this case the Cartagena Protocol on Biosafety which solely intends to avoid "adverse effects on the conservation and sustainable use of biological diversity" (CP Art. 1).	Comment noted.
Expert committees of DFG	57-60	46-Section 6.1	There is a lack of a clear definition of what is considered synthetic biology. This leads to a confusion of synthetic biology applications with classical GMOs and with conventional genetic engineering.	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).

GJSG on SynBio	57-60	46-Section 6.1	The lack of a clear definition of synthetic biology leads to confusing synthetic biology applications with classical conventional genetic engineering.	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).
Global Industry Coalition	58	10	**Delete** "*unprecedented*"	Editorial suggestion noted and text modified.
PRRI	58	10-12	Experience with release of biocontrol agents is useful and it offers a comparable scenario in terms of assessment of potential impacts before deploying them. In addition, several different types of gene drives are possible with different degrees of risks, and they cannot be generalized in terms challenges for the RA&M. There are a number of activities related to evaluate RA&M adequacy and challenges to different types of gene drives as well as guidances (such as EFSA: 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 https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2020.6297); and the updated WHO - Guidance framework for testing of genetically modified mosquitoes, second edition	Comment noted and Revision made.

			https://www.who.int/publications/i/item/9789240025233 platforms for research. It is probably interesting to list the existing science-based RA&M guidance already available instead of vague perceptions.	
Outreach Network for Gene Drive Research	58	10-12	Characterisation of the risk assessment challenges as "unprecedented" is unwarranted, as potential comparators exist, such as bio-control agents. In addition, the conclusion at the end of the paragraph that risks cannot be adequately assessed seems to be contradicted by the rest of the text in that paragraph, which notes that relevant principles and methodology for risk assessment of gene drives exist. It is also not consistent with the conclusions reached by the World Health Organisation, The European Food Safety Authority, and the report on the risk assessment of living modified organisms prepared by Perseus on behalf of the Secretariat of the Convention on Biological Diversity.	Comment noted and Revision made.
Global Industry Coalition	58	10-12	**Revise** for factualness. The conclusion sentence in line 10-12 contradicts with the summary at the beginning of the paragraph [line 47, page 57 to line 7, page 58]. The authors are recommended to point out that experienced risk assessors (references provided in the beginning of the paragraph) are not identifying the same concerns as these identified by interest groups or civil society campaigners (last reference in the paragraph). **Insert** at the end of the sentence on line 12 "However, there are established risk assessment paradigms that could be utilised, such as the regulation of bio-control agents." at the end of the sentence.	Comment noted and Revision made.
UK EBLC	58	11	With respect to the statement: 'This opens unprecedented challenges for risk assessment, because for the first time we are faced with a technology whose potential ecological and health impacts cannot be adequately assessed without first deploying it (Sirinathsinghji 2019)'. Note that this is a non-peer reviewed privately published single author opinion article. We completely disagree that this is unique to gene drives: as stated in our general remarks (page 0, line 0), it could equally be applied to antibiotics, where resistance represents a considerable danger to health; it can also be applied to pesticide	Comment noted and Revision made.

			coated mosquito nets, which have driven the evolutionary spread of pesticide resistance in mosquitoes. It can indeed be applied to natural systems, where ecological impacts are only evident after-the-event, like rabbits in Australia. Recall of some technologies are simpler than others, but the lasting effects of ecological impact are not. Case-by-case risk assessment is important, but do not overstate the case of the 'uniqueness' of synthetic biology. Compared to many older chemical and physical technologies, synthetic biology offers the possibility of generating significantly more specific and bespoke solutions to challenging problems.	
Western Michigan University	58	11	However, there are useful risk assessment paradigms that could be mentioned here, such as the regulation of bio-control agents.	Comment noted and Revision made.
Third World Network	58	11-12	An interlinked challenge for gene drive RA to the issue of spread and persistence being their *raison d'etre,* is the lack of ability to mitigate, recall or reverse a gene drive release, as acknowledged by the latest AHTEG on RA/RM. Any release can thus not currently be controlled, fundamentally challenging the validity of a phased-approach, or reversed in the event of a gene drive release going awry. This sentence should thus be strengthened to acknowledge this. Suggested addition: *"Combined with the lack of mitigation strategies for recalling or reversing gene drive releases, such issues warrant additional steps in ant risk assessment process that can operationalise the precautionary principle, including the introduction of cut-off criteria early in the process that can be applied when uncertainty is too high to ensure against adverse impacts."* A key reference here is: Then C. (2020) Limits of Knowledge and Tipping Points in the Risk Assessment of Gene Drive Organisms. In: von Gleich A., Schröder W. (eds) Gene Drives at Tipping Points. Springer, Cham. https://doi.org/10.1007/978-3-030-38934-5_8 Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/	Comment noted and Revision made.

ETC Group	58	11-12	An interlinked challenge for gene drive RA to the issue of spread and persistence being their *raison d'etre,* is the lack of ability to mitigate, recall or reverse a gene drive release, as acknowledged by the latest AHTEG on RA/RM. Any release can thus not currently be controlled, fundamentally challenging the validity of a phased-approach, or reversed in the event of a gene drive release going awry (Then 2020). This sentence should thus be strengthened to acknowledge this. Suggested addition: "Combined with the lack of mitigation strategies for recalling or reversing gene drive releases, such issues warrant additional steps in ant risk assessment process that can operationalise the precautionary principle, including the introduction of cut-off criteria early in the process that can be applied when uncertainty is too high to ensure against adverse impacts." Then C. (2020) Limits of Knowledge and Tipping Points in the Risk Assessment of Gene Drive Organisms. In: von Gleich A., Schröder W. (eds) Gene Drives at Tipping Points. Springer, Cham. https://doi.org/10.1007/978-3-030-38934-5_8	Comment noted and Revision made.
Imperial College London	58	11-12	This is very generic. There will be uncertainties, however, it remains to be assessed on a case-by-case basis if those uncertainties are acceptable or not. There are risk assessments for biological control agents which could be mentioned here.	Comment noted and Revision made.
African Centre for Biodiversity	58	11-12	For Risk Assessments of gene drive organisms, an additional challenge is the issue of spread and persistence being their *raison d'etre,* is the lack of ability to mitigate, recall or reverse a gene drive release, as acknowledged by the latest AHTEG on RA/RM. Any release can thus not currently be controlled, fundamentally challenging the validity of a phased-approach, or reversed in the event of a gene drive release going awry (Then 2020). This sentence should thus be strengthened to acknowledge this. Suggested addition: "Combined with the lack of mitigation strategies for recalling or reversing gene drive releases, such issues warrant additional steps in ant risk assessment process that can operationalise the precautionary principle, including the introduction of cut-off criteria early in the process that can be applied when uncertainty is too high to ensure against adverse impacts."	Comment noted and Revision made.

			Then C. (2020) Limits of Knowledge and Tipping Points in the Risk Assessment of Gene Drive Organisms. In: von Gleich A., Schröder W. (eds) Gene Drives at Tipping Points. Springer, Cham. https://doi.org/10.1007/978-3-030-38934-5_8 Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/	
Imperial College London	58	15-18	This requires a reference	Comment noted.
Western Michigan University	58	23	The references proposing that existing risk assessment methodologies may be applicable should be listed rather than given this superficial acknowledgment. There is no recognition that there is a legitimate difference of opinion on this point.	Comment noted.
Global Industry Coalition	58	23-29	**Revise** for factualness. Insert references to support the fact that the general principles and the case by case approach in existing risk assessment methodologies remain applicable for such organisms. It is recommended that the authors place the specific challenges identified in relation to organisms containing engineered gene drive in the context of the general risk assessment methodology as captured in Annex III of the Cartagena Protocols which states that "*The process of risk assessment may on the one hand give rise to a need for further information about specific subjects, which may be identified and requested during the assessment process, while on the other hand information on other subjects may not be relevant in some instances*". This will introduce the needed balance to this biased text.	Comment noted.
Third World Network	58	28	We disagree that a lack of validated modelling tools is the issue *per se*, rather it's that modelling can never be validated without empirical testing, which would require deployment or release into the environment. As such, it is a perverse situation where deployment would inform on the validity of a	Comment noted and Revision made.

			model, rather than the model informing on the implications of deployment. With fundamental knowledge gaps on background information for modelling parameters, it is currently entirely inadequate to rely on modelling for technologies designed to be released into wild propagating species, as acknowledged by the last AHTEG on RA/RM. Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/	
ETC Group	58	28	We disagree that a lack of validated modelling tools is the issue *per se*, rather it's that modelling can never be validated without empirical testing, which would require deployment or release into the environment. As such, it is a perverse situation where deployment would inform on the validity of a model, rather than the model informing on the implications of deployment. With fundamental knowledge gaps on background information for modelling parameters, it is currently entirely inadequate to rely on modelling for technologies designed to be released into wild propagating species, as acknowledged by the last AHTEG on RA/RM. It would be appropriate here to mention that a moratorium on gene drive field releases has been demanded by many civil society organisations (ETC Group 2018, Bassey-Orovwuje et al. 2019). Bassey-Orovwuje, M., Thomas, J. & Wakeford, T. Exterminator Genes: The Right to Say No to Ethics Dumping. Development 62, 121–127 (2019). https://doi.org/10.1057/s41301-019-00214-3 ETC Group 2018 United Nations Hits the Brakes on Gene Drives. https://www.etcgroup.org/content/united-nations-hits-brakes-gene-drives Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/	Comment noted and Revision made.
African Centre for Biodiversity	58	28	We would disagree that the lack of validated modelling tools is the main issue here, and rather it is the fact that modelling itself cannot be validated without	Comment noted and Revision made.

			empirical testing which requires the release into the environment. With fundamental knowledge gaps on background information for modelling parameters, it is currently entirely inadequate to rely on modelling for technologies designed to be released into wild propagating species, as acknowledged by the last AHTEG on RA/RM. (Sirinathsinghji, 2020) This has led to widespread calls for a moratorium on gene drive field releases has been demanded by many civil society organisations (ETC Group 2018, Bassey-Orovwuje et al. 2019). Bassey-Orovwuje, M., Thomas, J. & Wakeford, T. Exterminator Genes: The Right to Say No to Ethics Dumping. Development 62, 121–127 (2019). https://doi.org/10.1057/s41301-019-00214-3 ETC Group 2018 United Nations Hits the Brakes on Gene Drives. https://www.etcgroup.org/content/united-nations-hits-brakes-gene-drives Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/	
Imperial College London	58	29	Lack of experience and capacity – who does this refer to?	Comment noted. The source for the text is from the 2020 report of the AHTEG on risk assessment and risk management. See Section 6.1.1.
Global Industry Coalition	58	33	What is the “complexity of organisms” referring to?	Comment noted and Revision made.
Imperial College London	58	33-35	That depends on the construct and the released environment	Comment noted and Revision made.
African Centre for Biodiversity	58	33-35	The point on whether risk assessment could be sufficiently reliable with regard to biosafety risks of gene drives is critical and could be strengthened with further detail, including the biological novelty of gene drive organisms	Comment noted.

			carrying genetic engineering machinery to perform genetic engineering in each generation, in wild propagating populations. As a consequence, next-generation effects are of high concern, as noted by the last AHTEG on RA/RM. Therefore this could be rephrased accordingly: Due to the complexity of organisms containing engineered gene drives and its interaction with the environment and the biological novelty of including genetic engineering machinery into drive organisms (Simon et al., 2018), questions have been raised concerning whether risk assessment could result in sufficiently reliable conclusions due to the potential for next generation effects in wild, propagating populations (Dolezol et al., 2020). Inclusion of cut-off criteria into the risk assessment process has been proposed to be used when uncertainty is too high to ensure it is sufficiently reliable, as a means to operationalise the precautionary principle. A key reference here is: Then C. (2020) Limits of Knowledge and Tipping Points in the Risk Assessment of Gene Drive Organisms. In: von Gleich A., Schröder W. (eds) Gene Drives at Tipping Points. Springer, Cham. https://doi.org/10.1007/978-3-030-38934-5_8 Simon S, Otto M and Engelhard M (2018). Synthetic Gene Drive: Between Continuity and Novelty. EMBO Reports, 19(5). https://doi.org/10.15252/embr.201845760 Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/	
Third World Network	58	33-35	This point on whether risk assessment could be sufficiently reliable is critical with regard to biosafety risks of gene drives and could be strengthened with further detail, including the biological novelty of gene drive organisms carrying genetic engineering machinery to perform genetic engineering in	Comment noted.

			each generation, in wild propagating populations. As a consequence, next-generation effects are of high concern, as noted by the last AHTEG on RA/RM. *Due to the complexity of organisms containing engineered gene drives and its interaction with the environment and the biological novelty of including genetic engineering machinery into drive organisms (Simon et al., 2018), questions have been raised concerning whether risk assessment could result in sufficiently reliable conclusions due to the potential for next generation effects in wild, propagating populations (Dolezol et al., 2020). Inclusion of cut-off criteria into the risk assessment process has been proposed to be used when uncertainty is too high to ensure it is sufficiently reliable, as a means to operationalise the precautionary principle (Bauer-Pankus et al., 2020).* A key reference here is: Then C. (2020) Limits of Knowledge and Tipping Points in the Risk Assessment of Gene Drive Organisms. In: von Gleich A., Schröder W. (eds) Gene Drives at Tipping Points. Springer, Cham. https://doi.org/10.1007/978-3-030-38934-5_8 Simon S, Otto M and Engelhard M (2018). Synthetic Gene Drive: Between Continuity and Novelty. EMBO Reports, 19(5). https://doi.org/10.15252/embr.201845760 Sirinathsinghji (2020) Risk Assessment Challenges of Synthetic Gene Drive Organisms. Third World Network Biosafety Briefing. https://biosafety-info.net/articles/assessment-impacts/risk-assessment/risk-assessment-challenges-of-synthetic-gene-drive-organisms/	
ETC Group	58	34	We strongly support this acknowledgement that risk assessments based on lab experiments and modelling cannot be relied upon (same references as p.58, line 28).	Comment noted.
African Centre for Biodiversity	58	34	We strongly support this acknowledgement that risk assessments based on lab experiments and modelling cannot be relied upon (same references as p.58, line 28).	Comment noted.
CDTBE-UK	58	35	The report does not mention risk assessment strategies and outcomes for existing technologies, such as widespread pesticide use. It is important to recognise that existing methods, such as widespread utilisation of pesticide-	Comment noted.

			laden mosquito nets, carry with them their own risks, and these must also be considered in the risk assessment of applications such as gene drives. Whilst the complexity of the mosquito and its environment are significant the report fails to mention that existing technologies, which are already deployed at scale, are also making an impact.	
CDTBE-UK	58	34-35	Risk assessment for gene drives and bioengineered solutions are hard, but risk assessments for blunt instrument technologies, such as widespread pesticide use, are harder. One of the main advantages of pursuing an engineering biology approach to solving problems such as the malaria issue is that of precision. Gene drives (as an example) will target only a single species, and induce a well-defined effect in that population, limiting the number of variables and interactions that must be considered when assessing failure modes and performing risk assessment. This is in contrast to pesticides, which might have primary off-target impact upon multiple species, both through direct contact and by leaching into the environment from discarded mosquito nets. Secondary impacts due to, for example, bioaccumulation (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6140630/) or ecosystem disruption via the impact of primary off-target effects, might also present problems.	Comment noted.
Outreach Network for Gene Drive Research	58	37-38	Text should be added recognizing that modelling is a standard part of current risk assessments and not a novel practice unique to the assessment of gene drives.	Comment noted and Revision made.
Global Industry Coalition	58	37-38	**Please add comment** that the use of modelling in risk assessment is not novel	Comment noted and Revision made.
Western Michigan University	58	38-39	Suggested rewrite: change " limited in time and space and therefore provide data from small-scale tests that can be relevant to large-scale releases," to "...confined in time and space during small-scale tests, which allows the generation of data in those tests that can be relevant to large-scale releases,"	Editorial suggestions noted and Revision made.

Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	58	38-39	The intention of this sentence is unclear. Does it refer to natural gene drives? If those are limited in time and space, which might be an artefact and does not reflect the full scope of possibilities from natural gene drives, as successful and thus inactive natural gene drives are hard to identify and study. It is unclear if and how many species went extinct by natural gene drives, also known as selfish genes or selfish elements (Giese et al. 2019). Giese, Bernd; Frieß, Johannes L.; Barton, Nicholas H.; Messer, Philipp W.; Débarre, Florence; Schetelig, Marc F. et al. (2019): Gene Drives: Dynamics and Regulatory Matters-A Report from the Workshop "Evaluation of Spatial and Temporal Control of Gene Drives," April 4-5, 2019, Vienna. In: BioEssays : news and reviews in molecular, cellular and developmental biology, e1900151. DOI: 10.1002/bies.201900151.	Comment noted.
PRRI	58	38-41	There are different categories of gene drives under development, some approaches are intended to remain spatially restricted around the area of release, whereas other approaches are intended to distribute widely among interbreeding populations. The extent of spatial spread will be influenced by persistence characteristics. For instance the daisy chain gene drive system stops after a programmed number of generations.	Comment noted and Revision made.
Imperial College London	58	38-41	Self-limiting gene drives that are spatially and temporally limited are in development (e.g. daisy chains, split drives). Noble C, Min J, Olejarz J, Buchthal J, Chavez A, Smidler AL, DeBenedictis EA, Church GM, Nowak MA, Esvelt KM. Daisy-chain gene drives for the alteration of local populations. Proc Natl Acad Sci U S A. 2019 Apr 23;116(17):8275-8282. doi: 10.1073/pnas.1716358116. Epub 2019 Apr 2. PMID: 30940750; PMCID: PMC6486765.	Revision made.
Global Industry Coalition	58	40	**Insert** "(*depending on the type of drive*)" after "*areas*"	Editorial suggestion noted Revision made.
Imperial College London	58	42-43	There is no engineered gene drive that is close to a potential release. Any Gene drives developed which show promise to achieve for example population suppression base don laboratory experiments are still under research and development.	Comment noted.

Global Industry Coalition	58	45-49	**Revise** for completeness. The authors present the discussion about regulation of genome editing as part of the discussions on synthetic biology. This is misleading, as we have noted in other parts of this review. If retained, the text should be developed further by adding information on who is holding different views. It will help the readers of the document to understand what are the approaches taken by regulatory bodies and risk assessment bodies, what are the views of scientific bodies, and what are the views of interest and civil society groups.	See scope and methods.
Global Industry Coalition	58	46	**Insert** *"because the changes are equivalent to those that already exist (via conventional breeding or transgenesis) and for which there is a history of safe use"* after "*negligible risks*"	Comment noted.
Max Planck Institute for Terrestrial Microbiology	58	47 ff	The claim that genome editing allows for modifications that would not otherwise naturally arise is in complete ignorance of the entire body of knowledge regarding Darwin's theory of evolution by means of natural selection. The cited work grossly misrepresents statements made in original research that is cited in support of these absurd claims. For example, Monroe, J. G., Srikant, T., Carbonell-Bejerano, P., Exposito-Alonso, M., Weng M.-L., Rutter, M. T., Fenster, C. B., and Weigel, D. (2020) Mutation bias shapes gene evolution in *Arabidopsis thaliana*. bioRxiv 156752 https://doi.org/10.1101/2020.06.17.156752, states that mutations are less likely at some sites in the genome than others but does not claim that mutations at some sites are impossible, as misrepresented by the Kawall et al. reference cited in the report (Kawall, K., Cotter, J., & Then, C. (2020). Broadening the GMO risk assessment in the EU for genome 6 editing technologies in agriculture. Environmental Sciences Europe, 32(1), 106. 7 https://doi.org/10.1186/s12302-020-00361-2).	Revision made.
Third World Network	58	47-49	A further key reference should be included here: This 2021 EFSA opinion paper considered SDN1 genome editing applications, with the example of the low-gluten wheat variety, to induce complex patterns of genetic change that go beyond what can be achieved with conventional breeding and genetic	Revision made.

			engineering techniques to date. EFSA Panel on Genetically Modified Organisms (EFSA GMO Panel). Evaluation of existing guidelines for their adequacy for the molecular characterisation and environmental risk assessment of genetically modified plants obtained through synthetic biology (2021). https://doi.org/10.2903/j.efsa.2021.6301	
ISF	58/59	44 ff	Section 6.1.2 discusses the regulation of genome editing as if genome editing was equivalent with synthetic biology which is misleading and needs to be revised. Please provide more context as to how regulatory approaches differ and how this is relevant regarding synthetic biology.	See scope and methods.
Third World Network	59	03-05	The statement that unintended changes are not unique to genome editing and expected to be significantly lower than rates of spontaneous mutations or chemical mutagenesis, is omitting accumulating evidence of a wide array of unintended effects including on-target translocations, rearrangements, large-scale deletions and insertions, including insertion of exogenous DNA (and RNA-derived DNA templates) into edited cells, and the high-frequency production of aberrant proteins (e.g. Bruner et.al., (2019; Kosicki et al., (2018); Tulhadar et al.,(2019)). Moreover, evidence is accumulating that contradicts the assumption that nuclease-induced DNA breaks are repaired equivalently to naturally arising mutations, with evidence of increased levels of erroneous repair (Brinkman et al., 2018), and deployment of error-prone alternative DNA pathways not prescribed as resulting in SDN-1, 2 or 3 outcomes as widely assumed including alternative end joining and or combined with RNA-mediated DNA repair (Liu et al., 2021; van Overbeek et al; Ono et al., 2015). Unintended genomic changes are not routinely assessed, and are often missed unless more thorough analyses are performed. *This sentence should thus be removed, or altered to reflect the accumulating evidence that goes against the assertion that imprecision of genome editing is lower than natural mutations or classical mutagenesis, and instead reflects potential risks to biodiversity, and human health as a result of unintended changes at the level of the genome*.	Comments noted and Revision made.

			Brinkman, E. K., Chen, T., de Haas, M., Holland, H. A., Akhtar, W., & van Steensel, B. (2018). Kinetics and Fidelity of the Repair of Cas9-Induced Double-Strand DNA Breaks. Molecular Cell, 70(5), 801-813.e6. https://doi.org/10.1016/j.molcel.2018.04.016 Bruner E, Yagi R, Debrunner M, Beck-Schneider D, Burger A, Escher E, Mosimann C, Hausmann G and Basler K (2019). CRISPR-induced double-strand breaks trigger recombination between homologous chromosome arms. Life Sci Alliance 2(3), pii: e201800267 Kosicki M, Tomberg K and Bradley A (2018). Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. Nat Biotechnol 36, 765-771 Leibowitz ML, Papathanasiou S, Doerfler PA, Blaine LJ, Sun L, Yao Y, Zhang CZ, Weiss MJ, Pellman D (2021). Chromothripsis as an on-target consequence of CRISPR-Cas9 genome editing. Nature Genetics. 53(6):895-905. doi: 10.1038/s41588-021-00838-7. Liu, M., Zhang, W., Xin, C., Yin, J., Shang, Y., Ai, C., Li, J., Meng, F., & Hu, J. (2021). Global detection of DNA repair outcomes induced by CRISPR-Cas9 [Preprint]. Genomics. https://doi.org/10.1101/2021.02.15.431335 Ono, R., Ishii, M., Fujihara, Y., Kitazawa, M., Usami, T., Kaneko-Ishino, T., Kanno, J., Ikawa, M., & Ishino, F. (2015). Double strand break repair by capture of retrotransposon sequences and reverse-transcribed spliced mRNA sequences in mouse zygotes. Scientific Reports, 5, 12281. https://doi.org/10.1038/srep12281 Tuladhar R, Yeu Y, Tyler Piazza J, Tan Z, Clemenceau JR, Wu X, Barrett Q, Herbert J, Mathews DH, Kim J, Hwang TH and Lum L (2019). CRISPR-Cas9-based mutagenesis frequently provokes on-target mRNA misregulation. Nat Commun 10, 4056, doi: 10.1038/ s41467-019-12028-5 van Overbeek, M., Capurso, D., Carter, M. M., Thompson, M. S., Frias, E., Russ, C., Reece-Hoyes, J. S., Nye, C., Gradia, S., Vidal, B., Zheng, J., Hoffman, G. R., Fuller, C. K., & May, A. P. (2016). DNA Repair Profiling Reveals Nonrandom Outcomes at Cas9-Mediated Breaks. Molecular Cell, 63(4), 633–646. ENSSER (2021) "Scientific critique of Leopoldina and EASAC statements	

			on genome edited plants in the EU": https://ensser.org/wp-content/uploads/2021/04/Greens-EFA-GMO-Study-1.pdf	
ETC Group	59	03-05	The statement that unintended changes are not unique to genome editing and expected to be significantly lower than rates of spontaneous mutations or chemical mutagenesis, is omitting accumulating evidence of a wide array of unintended effects including on-target translocations, rearrangements, large-scale deletions and insertions, including insertion of exogenous DNA (and RNA-derived DNA templates) into edited cells, and the high-frequency production of aberrant proteins (e.g. Bruner et.al., (2019; Kosicki et al., (2018); Tulhadar et al.,(2019)). Moreover, evidence is accumulating that contradicts the assumption that nuclease-induced DNA breaks are repaired equivalently to naturally arising mutations, with evidence of increased levels of erroneous repair (Brinkman et al., 2018), and deployment of error-prone alternative DNA pathways not prescribed as resulting in SDN-1, 2 or 3 outcomes as widely assumed including alternative end joining and or combined with RNA-mediated DNA repair (Liu et al., 2021; van Overbeek et al; Ono et al., 2015). Unintended genomic changes are not routinely assessed, and are often missed unless more thorough analyses are performed. This sentence should thus be removed, or altered to reflect the accumulating evidence that goes against the assertion that imprecision of genome editing is lower than natural mutations or classical mutagenesis, and instead reflects potential risks to biodiversity, and human health as a result of unintended changes at the level of the genome. Brinkman, E. K., Chen, T., de Haas, M., Holland, H. A., Akhtar, W., & van Steensel, B. (2018). Kinetics and Fidelity of the Repair of Cas9-Induced Double-Strand DNA Breaks. Molecular Cell, 70(5), 801-813.e6. https://doi.org/10.1016/j.molcel.2018.04.016 Bruner E, Yagi R, Debrunner M, Beck-Schneider D, Burger A, Escher E, Mosimann C, Hausmann G and Basler K (2019). CRISPR-induced double-strand breaks trigger recombination between homologous chromosome arms. Life Sci Alliance 2(3), pii: e201800267 Kosicki M, Tomberg K and Bradley A (2018). Repair of double-strand breaks	Comments noted and Revision made.

			induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. Nat Biotechnol 36, 765-771 Leibowitz ML, Papathanasiou S, Doerfler PA, Blaine LJ, Sun L, Yao Y, Zhang CZ, Weiss MJ, Pellman D (2021). Chromothripsis as an on-target consequence of CRISPR-Cas9 genome editing. Nature Genetics. 53(6):895-905. doi: 10.1038/s41588-021-00838-7. Liu, M., Zhang, W., Xin, C., Yin, J., Shang, Y., Ai, C., Li, J., Meng, F., & Hu, J. (2021). Global detection of DNA repair outcomes induced by CRISPR-Cas9 [Preprint]. Genomics. https://doi.org/10.1101/2021.02.15.431335 Ono, R., Ishii, M., Fujihara, Y., Kitazawa, M., Usami, T., Kaneko-Ishino, T., Kanno, J., Ikawa, M., & Ishino, F. (2015). Double strand break repair by capture of retrotransposon sequences and reverse-transcribed spliced mRNA sequences in mouse zygotes. Scientific Reports, 5, 12281. https://doi.org/10.1038/srep12281 Tuladhar R, Yeu Y, Tyler Piazza J, Tan Z, Clemenceau JR, Wu X, Barrett Q, Herbert J, Mathews DH, Kim J, Hwang TH and Lum L (2019). CRISPR-Cas9-based mutagenesis frequently provokes on-target mRNA misregulation. Nat Commun 10, 4056, doi: 10.1038/ s41467-019-12028-5 van Overbeek, M., Capurso, D., Carter, M. M., Thompson, M. S., Frias, E., Russ, C., Reece-Hoyes, J. S., Nye, C., Gradia, S., Vidal, B., Zheng, J., Hoffman, G. R., Fuller, C. K., & May, A. P. (2016). DNA Repair Profiling Reveals Nonrandom Outcomes at Cas9-Mediated Breaks. Molecular Cell, 63(4), 633–646. ENSSER (2021) "Scientific critique of Leopoldina and EASAC statements on genome edited plants in the EU": https://ensser.org/wp-content/uploads/2021/04/Greens-EFA-GMO-Study-1.pdf	
African Centre for Biodiversity	59	03-05	The statement that unintended changes are not unique to genome editing and expected to be significantly lower than rates of spontaneous mutations or chemical mutagenesis, omits accumulating and overwhelming evidence of a wide array of unintended effects including on-target translocations, rearrangements, large-scale deletions and insertions, including insertion of exogenous DNA (and RNA-derived DNA templates) into edited cells, and the	Comments noted and Revision made.

			high-frequency production of aberrant proteins (e.g. Bruner et.al., (2019; Kosicki et al., (2018); Tulhadar et al.,(2019)). Moreover, evidence is accumulating that contradicts the assumption that nuclease-induced DNA breaks are repaired equivalently to naturally arising mutations, with evidence of increased levels of erroneous repair (Brinkman et al., 2018), and deployment of error-prone alternative DNA pathways not prescribed as resulting in SDN-1, 2 or 3 outcomes as widely assumed including alternative end joining and or combined with RNA-mediated DNA repair (Liu et al., 2021; van Overbeek et al; Ono et al., 2015). Unintended genomic changes are not routinely assessed, and are often missed unless more thorough analyses are performed. This sentence should thus be removed, or altered to reflect the accumulating evidence that goes against the assertion that imprecision of genome editing is lower than natural mutations or classical mutagenesis, and instead reflects potential risks to biodiversity, and human health as a result of unintended changes at the level of the genome. Brinkman, E. K., Chen, T., de Haas, M., Holland, H. A., Akhtar, W., & van Steensel, B. (2018). Kinetics and Fidelity of the Repair of Cas9-Induced Double-Strand DNA Breaks. Molecular Cell, 70(5), 801-813.e6. https://doi.org/10.1016/j.molcel.2018.04.016 Bruner E, Yagi R, Debrunner M, Beck-Schneider D, Burger A, Escher E, Mosimann C, Hausmann G and Basler K (2019). CRISPR-induced double-strand breaks trigger recombination between homologous chromosome arms. Life Sci Alliance 2(3), pii: e201800267 Kosicki M, Tomberg K and Bradley A (2018). Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. Nat Biotechnol 36, 765-771 Leibowitz ML, Papathanasiou S, Doerfler PA, Blaine LJ, Sun L, Yao Y, Zhang CZ, Weiss MJ, Pellman D (2021). Chromothripsis as an on-target	

			consequence of CRISPR-Cas9 genome editing. Nature Genetics. 53(6):895-905. doi: 10.1038/s41588-021-00838-7. Liu, M., Zhang, W., Xin, C., Yin, J., Shang, Y., Ai, C., Li, J., Meng, F., & Hu, J. (2021). Global detection of DNA repair outcomes induced by CRISPR-Cas9 [Preprint]. Genomics. https://doi.org/10.1101/2021.02.15.431335 Ono, R., Ishii, M., Fujihara, Y., Kitazawa, M., Usami, T., Kaneko-Ishino, T., Kanno, J., Ikawa, M., & Ishino, F. (2015). Double strand break repair by capture of retrotransposon sequences and reverse-transcribed spliced mRNA sequences in mouse zygotes. Scientific Reports, 5, 12281. https://doi.org/10.1038/srep12281 Tuladhar R, Yeu Y, Tyler Piazza J, Tan Z, Clemenceau JR, Wu X, Barrett Q, Herbert J, Mathews DH, Kim J, Hwang TH and Lum L (2019). CRISPR-Cas9-based mutagenesis frequently provokes on-target mRNA misregulation. Nat Commun 10, 4056, doi: 10.1038/ s41467-019-12028-5 van Overbeek, M., Capurso, D., Carter, M. M., Thompson, M. S., Frias, E., Russ, C., Reece-Hoyes, J. S., Nye, C., Gradia, S., Vidal, B., Zheng, J., Hoffman, G. R., Fuller, C. K., & May, A. P. (2016). DNA Repair Profiling Reveals Nonrandom Outcomes at Cas9-Mediated Breaks. Molecular Cell, 63(4), 633–646. ENSSER (2021) "Scientific critique of Leopoldina and EASAC statements on genome edited plants in the EU": https://ensser.org/wp-content/uploads/2021/04/Greens-EFA-GMO-Study-1.pdf	
CDTBE-UK	59	07-08	The larger the genome, the greater the risk of unintended effects by any modification scheme, be that by spontaneous mutation, traditional mutagenesis, or precision editing. In crops with large genomes, precision editing is still more precise than traditional techniques. The last sentence here is phrased as an argument against precision engineering, when it should not	Comment noted.

			be. It misrepresents the fact that for any given crop, editing by modern precision techniques is safer than by traditional ones. Consideration of the risk of off-target effects is only relevant when discussing different editing methods on the same organism.	
Western Michigan University	59	07-08	This concern is addressed during the standard crop development process, since deleterious effects of off-target editing would normally be detected during the development and testing process, and during the generation of field data for agronomic characterization and food safety evaluations consistent with the guidelines of the Codex Alimentarius. (Codex Alimentarius - Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants. FAO/WHO, 2003.) Therefore, this issue is no different from current LMO plants. Furthermore, research in ongoing that increases specificity of the nuclease used in editing.	Comments noted.
IWF	59	12	The sentence needs to elaborate more on the concern on criticisms	Comment noted.
CDTBE-UK	59	12-13	No mention of what criticisms have been levelled at untargeted metabolomics.	Comment noted.
Global Industry Coalition	59	12-13	**Revise** for factualness. The reference to the Court of Justice of the European Union, 2018, is questionable and should be deleted.	Comment noted and Revision made.
ETC Group	59	15	We strongly reject the suggestion that a "Risk assessment light" could be used for the regulation of genome editing due to many uncertainties in the edited crop constructions, as well as the high likelihood that, like in the case of GMOs, it could cause harm to the environment, crop relatives and the health of peasant farmers and ultimately consumers.	Comment noted.
African Centre for Biodiversity	59	15	We strongly reject the suggestion that a "Risk assessment light" could be used for the regulation of genome editing due to many uncertainties in the edited crop constructions, as well as the high likelihood that, like in the case of GMOs, it could cause harm to the environment, crop relatives and the health of peasant farmers and ultimately consumers.	Comment noted.

Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	59	15-16	” For example, a “risk assessment light” could be implemented for cases with minimal changes and familiarity with the particular trait or plant of use (Eckerstorfer, Dolezel, et al., 2019;Schiemann etal. “ I do not see this statement fully supported by Eckerstorfer et al 2019, as this publication rather intents to warn against assuming the safety of nGM plants without the appropriate data from a sound risk assessment. Please consider identifying a more appropriate reference.	Commend noted and Revision made.
CDTBE-UK	59	23-24	Precision of a technique is not an indication of safety of the resultant modified organism. However, this closing sentence fails to address that the targeted nature of precision editing increases the likelihood that any and all off-target effects will be discovered under a given testing regimes compared to less precise traditional techniques. The extra precision increases our confidence in safety under a given testing regime.	Comment noted.
PRRI	59	26	Discussion on genome editing organisms potential benefits and risks are being discussed for a long time. Some countries already have clear rules which genome edited organisms are covered by the regulations.	Comment noted see Section 7.1.1.
Third World Network	59	30-32	With regard to the presence of exogenous DNA not being present in SDN-1 or -2 applications, this assumption has now been proven to be incorrect. Multiple studies have detected the insertion of exogenous DNA. As such, we suggest additional sentences to incorporate these findings: “*However, exogenous DNA has been detected in genome edited organisms, and would require detailed assessments to ensure that they are indeed free of unintended exogenous genetic insertions (Biswas et al., 2020; Liu et al., 2021; Norris et al., 2020; Ono et al., 2019; Roberts et al., 2017; Q. Zhang et al., 2018)*”. Biswas, S., Tian, J., Li, R., Chen, X., Luo, Z., Chen, M., Zhao, X., Zhang, D., Persson, S., Yuan, Z., & Shi, J. (2020). Investigation of CRISPR/Cas9-induced SD1 rice mutants highlights the importance of molecular characterization in plant molecular breeding. Journal of Genetics and Genomics, S1673852720300916. Liu, M., Zhang, W., Xin, C., Yin, J., Shang, Y., Ai, C., Li, J., Meng, F., &	Comment noted and Revision made.

			Hu, J. (2021). Global detection of DNA repair outcomes induced by CRISPR-Cas9 [Preprint]. Genomics. https://doi.org/10.1101/2021.02.15.431335 Norris, A. L., Lee, S. S., Greenlees, K. J., Tadesse, D. A., Miller, M. F., & Lombardi, H. A. (2020). Template plasmid integration in germline genome-edited cattle. Nature Biotechnology, 38(2), 163–164. https://doi.org/10.1038/s41587-019-0394-6 Ono, R., Yasuhiko, Y., Aisaki, K., Kitajima, S., Kanno, J., & Hirabayashi, Y. (2019). Exosome-mediated horizontal gene transfer occurs in double-strand break repair during genome editing. Communications Biology, 2(1), 57. https://doi.org/10.1038/s42003-019-0300-2 Roberts, B., Haupt, A., Tucker, A., Grancharova, T., Arakaki, J., Fuqua, M. A., Nelson, A., Hookway, C., Ludmann, S. A., Mueller, I. A., Yang, R., Horwitz, R., Rafelski, S. M., & Gunawardane, R. N. (2017). Systematic gene tagging using CRISPR/Cas9 in human stem cells to illuminate cell organization. Molecular Biology of the Cell, 28(21), 2854–2874. https://doi.org/10.1091/mbc.E17-03-0209 Zhang, Q., Xing, H.-L., Wang, Z.-P., Zhang, H.-Y., Yang, F., Wang, X.-C., & Chen, Q.-J. (2018). Potential high-frequency off-target mutagenesis induced by CRISPR/Cas9 in Arabidopsis and its prevention. Plant Molecular Biology, 96(4–5), 445–456. https://doi.org/10.1007/s11103-018-0709-x	
African Centre for Biodiversity	59	30-32	With regard to the presence of exogenous DNA not being present in SDN-1 or -2 applications, this assumption has now been proven to be incorrect. Multiple studies have detected the insertion of exogenous DNA. As such, we suggest additional sentences to incorporate these findings: "However, exogenous DNA has been detected in genome edited organisms, and would require detailed assessments to ensure that they are indeed free of unintended exogenous genetic insertions (Biswas et al., 2020; Liu et al., 2021; Norris et al., 2020; Ono et al., 2019; Roberts et al., 2017; Q. Zhang et al., 2018)". Biswas, S., Tian, J., Li, R., Chen, X., Luo, Z., Chen, M., Zhao, X., Zhang, D., Persson, S., Yuan, Z., & Shi, J. (2020). Investigation of CRISPR/Cas9-	Comment noted and Revision made.

			induced SD1 rice mutants highlights the importance of molecular characterization in plant molecular breeding. Journal of Genetics and Genomics, S1673852720300916. Liu, M., Zhang, W., Xin, C., Yin, J., Shang, Y., Ai, C., Li, J., Meng, F., & Hu, J. (2021). Global detection of DNA repair outcomes induced by CRISPR-Cas9 [Preprint]. Genomics. https://doi.org/10.1101/2021.02.15.431335 Norris, A. L., Lee, S. S., Greenlees, K. J., Tadesse, D. A., Miller, M. F., & Lombardi, H. A. (2020). Template plasmid integration in germline genome-edited cattle. Nature Biotechnology, 38(2), 163–164. https://doi.org/10.1038/s41587-019-0394-6 Ono, R., Yasuhiko, Y., Aisaki, K., Kitajima, S., Kanno, J., & Hirabayashi, Y. (2019). Exosome-mediated horizontal gene transfer occurs in double-strand break repair during genome editing. Communications Biology, 2(1), 57. https://doi.org/10.1038/s42003-019-0300-2 Roberts, B., Haupt, A., Tucker, A., Grancharova, T., Arakaki, J., Fuqua, M. A., Nelson, A., Hookway, C., Ludmann, S. A., Mueller, I. A., Yang, R., Horwitz, R., Rafelski, S. M., & Gunawardane, R. N. (2017). Systematic gene tagging using CRISPR/Cas9 in human stem cells to illuminate cell organization. Molecular Biology of the Cell, 28(21), 2854–2874. https://doi.org/10.1091/mbc.E17-03-0209 Zhang, Q., Xing, H.-L., Wang, Z.-P., Zhang, H.-Y., Yang, F., Wang, X.-C., & Chen, Q.-J. (2018). Potential high-frequency off-target mutagenesis induced by CRISPR/Cas9 in Arabidopsis and its prevention. Plant Molecular Biology, 96(4–5), 445–456. https://doi.org/10.1007/s11103-018-0709-x	
Global Industry Coalition	59	36	**Revise** for factualness. Note that "*hazard*" is not the same as risk.	Comment noted and Revision made.

Global Industry Coalition	59	37-39	**Please add comment** that these "points to consider" are not unique to genome editing but can also apply to transgenesis.	Comment noted and Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	59	42	This section on animals would benefit from a view to the regulation in the US, where plants and animals are not regulated in an analogous way. The retention of transgenic DNA in genome edited cattle (Norris et al 2020) in this context is another example of why all genome edited LMOs require robust risk assessment Norris, A.L., Lee, S.S., Greenlees, K.J. et al. Template plasmid integration in germline genome-edited cattle. Nat Biotechnol 38, 163–164 (2020). https://doi.org/10.1038/s41587-019-0394-6	Comment noted.
Global Industry Coalition	59	46	"… *equivalent to changes expected from classical breeding*". Note that the same applies to plants.	Comment noted and Revision made.
Third World Network	59	46-47	We strongly disagree with the assertion that in cases of SDN-1, SDN-2 and ODM, the changes would be expected to be equivalent to classical breeding for genome edited animals. This point is related to the above points and references in regard to pg 59 lines 3-5 and 30-32, where we provide evidence to the contrary. To illustrate this, unintended effects of genome editing are not contested in the medical field. Risks of unintended effects such as the development of cancers and other forms of genetic damage that could be passed to future generations are directly relevant to animal breeding. Various animal studies, including mouse embryos, are also detecting unintended effects and should be added as references. National Academy of Medicine (U.S.), National Academy of Sciences (U.S.), & Royal Society (Great Britain) (Eds.). (2020).Heritable human genome editing. (the National Academies Press, 2020). Ledford, H. CRISPR gene editing in human embryos wreaks chromosomal mayhem. Nature 583, 17–18 (2020). Burgio, G. & Teboul, L. Anticipating and Identifying Collateral Damage in Genome Editing. Trends Genet. TIG 36, 905–914 (2020). It is not a lack of scientific data that gives rise biosafety concerns, but rather that there could be unintended effects that give rise to biosafety concerns.	Comment noted.

African Centre for Biodiversity	59	46-47	We strongly disagree with the assertion that in cases of SDN-1, SDN-2 and ODM, the changes would be expected to be equivalent to classical breeding for genome edited animals. To illustrate this, unintended effects of genome editing are not contested in the medical field. Risks of unintended effects such as the development of cancers and other forms of genetic damage that could be passed to future generations are directly relevant to animal breeding. It is not a lack of scientific data that gives rise biosafety concerns, but rather that there could be unintended effects that give rise to biosafety concerns. Various animal studies, including mouse embryos, are also detecting unintended effects and should be added as references. National Academy of Medicine (U.S.), National Academy of Sciences (U.S.), & Royal Society (Great Britain) (Eds.). (2020).Heritable human genome editing. (the National Academies Press, 2020). Ledford, H. CRISPR gene editing in human embryos wreaks chromosomal mayhem. Nature 583, 17–18 (2020). Burgio, G. & Teboul, L. Anticipating and Identifying Collateral Damage in Genome Editing. Trends Genet. TIG 36, 905–914 (2020).	Comment noted.
Global Industry Coalition	60	05-07	**Revise** for factualness. On line 7 "*others*" is used. Please review if more than one or just the risk assessor of the EU – EFSA? Several other regulators have not had issue assessing these types of LMOs.	Comment noted and Revision made.
IWF	60	11	Mention- source and reference, as most studies deflect this sentence.	Comment noted and Revision made.
Western Michigan University	60	11-12	This statement is incorrect. Plants using RNAi have been commercialized from the beginning of GMO crop development. In fact the first GMO plant product, Flavr Savr, was an example of RNAi technology (Krieger, Elysia K., Edwards Allen, Larry A. Gilbertson, James K. Roberts, William Hiatt, and Rick A. Sanders. "The Flavr Savr Tomato, an Early Example of RNAi Technology." HortScience 43, no. 3 (June 2008): 962–64. https://doi.org/10.21273/HORTSCI.43.3.962). Therefore, there are already	Comment noted and Revision made.

			risk assessment examples of RNAi, and RNAi GM crops are already among the commercialized suite of crops. Another early example is virus resistant papaya (Azad, Md. Abul Kalam, Latifah Amin, and Nik Marzuki Sidik. "Gene Technology for Papaya Ringspot Virus Disease Management." Edited by S. Rodtong and R. Dinkins. The Scientific World Journal 2014 (March 17, 2014): 768038. https://doi.org/10.1155/2014/768038). A recent example is the INNATE potato product of Simplot (https://www.simplot.com/news/innate_potato_receives_fda_safety_clearance).	
Global Industry Coalition	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.*". Risk assessment has been carried out by multiple regulatory agencies on a number of RNAi-based plant products and some have been commercialised. The authors are recommended to consult regulatory agencies' sites and product registration information to update their review.	Comment noted and Revision made.
Third World Network	60	15-17	Additional considerations include exposure to dietary RNAs from RNAi-based plants. Circulating diet-derived dsRNAs have been detected in mammals, raising biosafety concerns regarding exposure to dsRNAs expressed in plants, or external RNAi sprays, and also should be fully assessed, and not assumed to degrade during digestion. Wang, K., Li, H., Yuan, Y., Etheridge, A., Zhou, Y., Huang, D., Wilmes, P., & Galas, D. (2012). The complex exogenous RNA spectra in human plasma: an interface with human gut biota? PLOS ONE 7(12), e51009. https://doi.org/10.1371/journal.pone.0051009 Tomé-Carneiro, J., Fernández-Alonso, N., Tomás-Zapico, C., Visioli, F., Iglesias-Gutierrez, E., & Dávalos, A. (2018). Breast milk microRNAs harsh journey towards potential effects in infant development and maturation. Lipid encapsulation can help. Pharmacological Research, 132, 21–32.	Comment noted.
African Centre for Biodiversity	60	15-17	Additional considerations include exposure to dietary RNAs from RNAi-based plants. Circulating diet-derived dsRNAs have been detected in	Comment noted.

			mammals, raising biosafety concerns regarding exposure to dsRNAs expressed in plants, or external RNAi sprays, and also should be fully assessed, and not assumed to degrade during digestion. Wang, K., Li, H., Yuan, Y., Etheridge, A., Zhou, Y., Huang, D., Wilmes, P., & Galas, D. (2012). The complex exogenous RNA spectra in human plasma: an interface with human gut biota? PLOS ONE 7(12), e51009. https://doi.org/10.1371/journal.pone.0051009 Tomé-Carneiro, J., Fernández-Alonso, N., Tomás-Zapico, C., Visioli, F., Iglesias-Gutierrez, E., & Dávalos, A. (2018). Breast milk microRNAs harsh journey towards potential effects in infant development and maturation. Lipid encapsulation can help. Pharmacological Research, 132, 21–32.	
Global Industry Coalition	60	18-22	**Delete.** This is dated information, about dated technology, and too much detail about EFSA. Regulatory approvals were granted prior to the release of the first SB technical series.	Editorial suggestion noted. Revision made.
Global Industry Coalition	60	24-25	**Revise** for factualness. "…*how different regulators perceive novelty*" The text is this section falsely implies that risk assessment procedures are limited to one type of LMO. In reality, these can be applied to any LMO on a case-by-case basis.	Comment noted.
Global Industry Coalition	60	27	**Insert** *"therefore"* after "*systems"*	Editorial suggestion noted and revision made.
Global Industry Coalition	60	28	**Delete** "*Thus, it represents a novel*" and **replace with** "*Such products are a*"	Editorial suggestion noted and revision made.
Global Industry Coalition	60	29-30	**Delete "***it is important that safety assessments for plant protection products* are adapted to allow introductions of this technology" and replace with "their safety assessment as a plant protection product may be required for their introduction."	Comment noted.

ETC Group	60	32	We agree that additional research is necessary to assess the risk of these technologies before they are considered to be released into the environment.	Comment noted.
African Centre for Biodiversity	60	32	We agree that additional research is necessary to assess the risk of these technologies before they are considered to be released into the environment.	Comment noted.
CDTBE-UK	60	42	Need a space after the full stop "…2020). At …"	Editorial suggestion noted and revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	61	07	Please consider to delete „if deemed to be relevant" as issues concerning the stability of formulated RNA or the lack of reference genomes for bioinformatics off-target research are most likely of high relevance for biosafety assessment.	Editorial suggestion noted.
Max Planck Institute for Terrestrial Microbiology	61	7 ff	It is not clear how the discussion on "off-target" effects in plants with genomes of different sizes informs on specific risks. CrispR is in fact, a cleaner technology than classical mutagenesis (which is already proven safe and societally valuable with currently used crop varieties), and now with whole-genome sequencing, the genetic material considered in each case can be precisely evaluated. Further "Largely missing from this conversation, however, is attention to local communities in decision-making which are likely to be the first to feel any potential impact from these applications (Kofler et al., 2018)". It is unclear what type of cost that local communities will bear e.g. upon the cultivation of a maize CrispR line.	Comment noted.
Third World Network	61	24	We agree that it is important to include here the reference to needing to understand any epigenetic effects of RNAi technologies. However, it is also key that there is additional acknowledgement that epigenetic changes may be hereditary (see e.g. Heinemann, 2019). This point should be incorporated as it has important biosafety implications if effects can be multi-generational, as well as definitional implications for whether dsRNA exposed organisms are indeed an LMO. Heinemann J. A. (2019). Should dsRNA treatments applied in outdoor	Editorial suggestion noted and revision made.

			environments be regulated? Environment International, 132, 104856. https://doi.org/10.1016/j.envint.2019.05.050	
ETC Group	61	24	This should include the fact that epigenetic changes can be inherited, which is an additional risk to ecosystems and biodiversity.	Editorial suggestion noted and revision made.
African Centre for Biodiversity	61	24	We agree that it is important to include here the reference to needing to understand any epigenetic effects of RNAi technologies. However, it is also key that there is additional acknowledgement that epigenetic changes may be hereditary (see e.g. Heinemann, 2019). This point should be incorporated as it has important biosafety implications if effects can be multi-generational, as well as definitional implications for whether dsRNA exposed organisms are indeed an LMO. Heinemann J. A. (2019). Should dsRNA treatments applied in outdoor environments be regulated? Environment International, 132, 104856. https://doi.org/10.1016/j.envint.2019.05.050	Editorial suggestion noted and revision made.
Third World Network	61	32	Examples of "built-in safety features" are lacking.	Comment noted.
ETC Group	61	32	There are no current examples of "build-in safety features", only speculation. Also applies to "kill switches" (p.62 Line 11).	Comment noted. See sections 3.3.3 (d) and 6.2.2.
African Centre for Biodiversity	61	32	Examples of "built-in safety features" are lacking.	Comment noted. See sections 3.3.3 (d) and 6.2.2.
Global Industry Coalition	61-62	45-47, 01-20	**Delete** sections 6.2.1 and 6.2.2 – this is dated information and not new developments.	Editorial suggestion noted.
PRRI	62	01-11	Different strategies for biocontainment are being developed and improved, including kill-switches but not only.	Comment noted. See Section 6.2. for examples.
Western Michigan University	62	21	This section misses discussing strategies to limit spread via split or multi-component drives, which are biocontainment approaches, as opposed to the others described in this section and the next, which are designed to reverse a drive.	Revision made.

Outreach Network for Gene Drive Research	62	21	This section should also discuss multi-component and split drive approaches to biocontainment, which are distinct from the approaches intended to reverse a drive already included.	Revision made.
Global Industry Coalition	62	21	**Revise** for completeness. This section should also include a discussion of strategies to limit spread via split or multi-component drives, which are biocontainment approaches as opposed to the others described in the following section and the next, which are designed to reverse a drive.	Revision made.
Imperial College London	62	31-40	The use of localised high threshold (underdominance) and self-limiting drives (split drives, daisy chains and killer rescue) is missing.	Revision made.
JCVI	62, 63	21-46, 1-49	Subsections 6.2.3 and 6.2.4 discuss two topics related to gene drives: 1) designs for temporal and geographic containment and 2) post-release removal. The concepts are mixed into both sections in a confusing manner. Headings should clearly refer to gene drives, not generalize to "synthetic biology organisms."	Comment noted and Revision made..
Western Michigan University	63	31	There is no clear distinction between the mitigation strategies described in this section and those described in the previous section, since some examples in the previous section also act to reverse a drive that has already been released.	Comment noted and Revision made.
Imperial College London	63	35	These examples (e.g. daisy chains, underdominance) do not fall under the title for this section (post release removal)	Comment noted and Revision made.
Global Industry Coalition	64	04	**Replace** *"Current"* with *"Approved"*	Editorial suggestion noted and revision made.
PRRI	64	06-08	Genome editing techniques are not exclusive to synthetic biology and they should not be mixed.	Editorial suggestion noted and revision made.

Global Industry Coalition	64	08	**Delete** "*classical genetic engineering*" and **replace with** *"recombinant DNA approaches"*	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).
Global Industry Coalition	64	09	**Delete** *"synthetic"* **Insert** "if subject to GMO regulatory provisions" after "organisms"	Editorial suggestion noted and revision made.
Global Industry Coalition	64	18	**Insert** "*technically*" prior to "*feasible*".	Editorial suggestion noted and revision made.
JCVI	64	20	Given the extensive discussion of gene drive organisms, one might explicitly point out that such organisms are easily detected with PCR-based methods	Comment noted and Revision made.
ISF	64	27-31	The reference to Chhalliyil et al. (2020) is misleading. The method presented by the authors of that publication is incapable of identifying genome editing as the cause for a detected genetic variation and is thus invalid for detecting genome edited organisms. Moreover, the provided method cannot be generalized and appears to lack specificity since it also detects wild type canola and wild canola relatives as genome edited. Please delete reference to Chhalliyil et al. or provide correct context.	Comment noted.

			Statement of European Network of GMO Laboratories on Chhalliyil et. 2020 Statement of German BVL on Chhalliyil	
ZKBS	64	27-31	The methods described in Chhalliyil et al. 2020 and Peng et al. 2020 can specifically detect a point mutation introduced into a crop plant. However, these methods do not allow the identification of a genome-edited plant, because solely identifying a given point mutation does not allow to disclose the method used for the creation of specific point mutations. Consequently, the methods described in Chhalliyil and Peng do not allow for the discrimination between a genome-edited plant and a plant having acquired the same point mutation spontaneously or through traditional mutagenesis e.g. by radiation or chemical treatment of seeds. The following text, which is scientifically incorrect and grossly misleading, should therefore be deleted: "Despite this concern, recent developments have demonstrated the potential possibility of detecting and quantifying genome edited canola and rice utilising real-time quantitative PCR and droplet digital PCR, respectively (Chhalliyil et al., 2020; Peng et al., 2020). In particular, the method for detecting the genome edited oilseed rape demonstrated consistency with ISO1702532 standards (Chhalliyil et al., 2020)." For reference, please see the statement made by the ZKBS on its homepage (see https://www.zkbs-online.de/ZKBS/EN/Home/home_node.html à Commentaries).	Comment noted and Revision made.
Global Industry Coalition	64	31	**Insert** at the end of the sentence "*although these are isolated cases in seed materials and generalizations based on these cannot be made*." While the Chhalliyil reference shows that it is possible to detect a DNA change - it is not possible to distinguish whether the DNA change occurred as a result of genome editing or other breeding methods, or occurred spontaneously. For completeness, please add information from the publication: Evaluation of the scientific publication: "A Real-Time Quantitative PCR Method Specific for Detection and Quantification of the First Commercialized Genome-Edited Plant" P. Chhalliyil et al. in: Foods (2020) 9, 1245 by the European Network of GMO Laboratories (ENGL)	Comment noted.

Global Industry Coalition	64	32-33	**Insert** at the end of the sentence "…*or an artifact due to the specific reference genome used as the reference*". Again we question how this can be synthetic biology.	Comment noted.
Global Industry Coalition	64	33-36	**Insert** at the end of the sentence "… *or whether this difference is present in the general plant population*".	Comment noted.
Global Industry Coalition	64	40	**Insert** new sentence prior to "*Thus, to*…" *"In recombinant DNA approaches, screening of genetic elements is commonly used to identify materials (Morisset et al 2014). However, each edit will be unique, so that there will be no 'screening' strategy available for a range of products. This further increases the challenge of analyzing heterogeneous samples."* Reference: Morisset D, Novak PK, Zupanič D, Gruden K, Lavrač N, Žel J. GMOseek: a user friendly tool for optimized GMO testing. BMC Bioinformatics. 2014 Aug 1;15(1):258. doi: 10.1186/1471-2105-15-258.	Comment noted.
Third World Network	64	41-44	Information disclosure is important to a framework for identification and detection of genome edited products. The Ribartis et al. (2021) paper referred to proposes an anticipatory framework in the current situation of absence of uniform regulation of genome edited crops worldwide, involving voluntary information disclosure, making the case that detection and identification of such products is possible. If these products are regulated, then governments can of course more easily require this information of developers. The sentence should be clarified to reflect these elements.	Comment noted.
African Centre for Biodiversity	64	41-44	Information disclosure is important to a framework for identification and detection of genome edited products. The Ribartis et al. (2021) paper referred to proposes an anticipatory framework in the current situation of absence of uniform regulation of genome edited crops worldwide, involving voluntary information disclosure, making the case that detection and identification of such products is possible. If these products are regulated, then governments can of course more easily require this information of developers. The sentence should be clarified to reflect these elements.	Comment noted.

Global Industry Coalition	64	43	**Replace** "*organisms were regulated*" with "*organisms were to be regulated in the country or region where they are grown or imported*."	Comment noted, and Revision made.
Global Industry Coalition	64	45	**Add** at the end of the sentence "*However, the latter view assumes that there will be more sequence changes than typically seen in commercial products and does not consider the breeding and selection process involved in the development of a plant variety*."	Comment noted.
WHO	64		The status of implementation of ISO 35001:2019 could perhaps be checked and possible reflected on this page. See also CWA 15793.	Comment noted.
Global Industry Coalition	65	0	**General comment** – we note the authors comment that the "*magnitude of recent changes in the field of synthetic biology … are the main focus of the document*" (page 15, lines 28-29). However, half of this (lengthy) document is on the topic of "*Synthetic biology governance and regulatory perspectives*" (Section E), and this consists of substantial text that is simply copied directly from the 2015 technical series document, or is copied with minor changes and/or additions. This content could be greatly reduced by referring to the 2015 technical series and only providing relevant information that is actually an "update". For example (not exhaustive), Section 9.3.1 "Risk of harm" (from page 103 line 38 to page 108 line 23 – this is a direct copy from pages 76-80 of the 2015 document). Also, the entire information on "contained use" (page 88 – direct copy of pages 87-88 of the 2015 document); Codex Alimentarius (page 125 – direct copy of page 99 of the 2015 document); and the International Convention for the Protection of New Varieties of Plants (pages 118-120 – direct copy of pages 109-120 of the 2015 document). The sections on the Convention on Biological Diversity (Section 8.1), the Cartagena Protocol (Section 8.2) and the Nagoya Protocol (Section 8.4) are also substantially similar to the 2015 text.	Comment noted.
PRRI	65	01	There are no tools for exclusive use in synthetic biology, the tools can be used in different biotechnologies.	Comment noted.

Global Industry Coalition	65	07	**Add** at the end of the sentence "*However, adding such 'signatures' to organisms that have single or few nucleic acid changes is not feasible and defeats the object of making very small changes*."	Comment noted.
Global Industry Coalition	65	10	**Insert** new sentence prior to "*Further*…" *"However, it has not proven possible to differentiate proteins that have for example a single amino acid change, which is what many edits may result in, particularly if that change is in the active site of the protein."* Replace "Further is was proposed" with "It has been proposed"	Comment noted.
Global Industry Coalition	65	16	**Insert** *"currently"* after "*were"*	Editorial suggestion noted and Revision made.
DER VBIO & GASB	65ff	18ff	***"E. SYNTHETIC BIOLOGY GOVERNANCE AND REGULATORY PERSPECTIVES*** ***7.The Governance and Regulation of Synthetic Biology"*** ***In our view, the current vagueness of definition is not a good basis for deriving any regulatory consequences. This necessarily requires a prior definition of the subject of regulation.*** ***Ä We propose to postpone governance and regulatory perspectives (chapter E; pg. 65 to 120) until a mutually accepted definition, or several workable definitions, of synthetic biology are available.***	See background and scope and methods.
JCVI	65	19-32	This section needs an introduction to Section E, Synthetic Biology Governance. The section includes approximately 3 pages on national regulation, 3 pages on self governance, 20 pages on the CBD, and 30 pages on other international aspects of synthetic biology governance. As correctly stated on p.68, lines 29-30, the majority of regulatory decision-masking will be at the national level. Thus, the section needs an introduction that puts the three forms of governance into perspective. Otherwise, it is impossible to understand and contextualize the governance gaps and overlaps identified in	Revision made.

			the 50 pages devoted to international governance. Expanded discussions of national regulation and self governance would also be useful, if time permits.	
New Zealand - Centre for Integrated Research in Biosafety (CIRB)	65	20-32	I suggest that the paragraph be revised to separate these falsely conflated alternative viewpoints on the rationale for governance. The current document perpetuates a particular framing of the perspectives on (1) why gene technologies should be governed with (2) how (or why) they should be regulated. This is seen in the describing of the viewpoints as "biotechnological developments being inherently risky" or "these technologies not presenting any unique or novel risks". The former frames the rationale for risk assessment and the latter what is evaluated in a risk assessment, which are not different sides of the same coin. The inherent property of technology is that it changes the gearing ratio between human activity and the outcome of human activity (Heinemann et al. 2021). "Traditional breeding" is generally regarded as relatively slow compared to what can be achieved using gene technologies. The pace of traditional breeding defines the baseline condition of how much human effort is needed to change outcomes. Technology gears up the scale of change by human intervention and along with it the inseparable load of unintended outcomes that are possible because of the process or the product. That is why technology itself is a suitable trigger for regulation (a trigger provided by governance), as it is in a number of other cases where technology catalyses activity with grand geographical scale potential, such as nuclear power and weapons. The equivalent non-sequitur framing there would look like: "nuclear fission developments being inherently risky" or "these technologies not presenting any unique or novel risks" because after all atoms decay all the time in nature. The ability of human activity to align atoms with different energy potentials to create a chain reaction, and to concentrate the different species of atoms to achieve a threshold of explosive power, or even to just release radiation (weapons vs medical applications) is the reason why nuclear technology should be regulated. How it should be assessed for risk is then informed by what is expected to be the outcome of the technology (Heinemann et al. 2021).	Comment noted.

			In this regard, synthetic biology is like any other manifestation of gene technology.	
Brazilian Bar Association	65	20-32	The emerging area of Synthetic Biology has a similar evolution stage of other technologies developed in the past, such as genetically modified organism and genetic engineering, raising a wide range of ethical and political issues, divergent viewpoints and heterogeneous governance approaches in national legislation.	Comment noted.
New Zealand - CIRB	65	33-44	The above would align better with this paragraph which in essence is saying the use of syn bio will likely be assessed for risk. The question then is not whether to govern, but whether assessment currently is suited to predicting the likelihood of adverse effects from all applications of synthetic biology.	Comment noted.
Global Industry Coalition	65	35	**Delete** *"will"*	Editorial suggestion noted.
Global Industry Coalition	65	35	**Insert** *"a range of broader considerations, including "* after "*influenced by"*	Editorial suggestion noted and Revision made.
Global Industry Coalition	65	36	**Delete** "*considerations*" and **replace with** "*aspects*"	Editorial suggestion noted and Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	65	36-37	It should state "potential benefits". Also it should be made clear that this is explicitly not in the scope of CBD.	Editorial suggestion noted and Revision made.
EBRC	65	36-38	This is an important point. It also spurs recall of a point made on page # 16 that applications of synthetic biology and deployments of said applications should be considered on a case-by-case basis that include weighing the benefits of the application.	Comment noted.
Brazilian Bar Association	65	39	Brazilian Law 11.105/2005 provides for safety standards and inspection mechanisms for activities involving GMOs and their derivatives. In addition, RN CTNBio 16/ 2018 deals with genomic alterations arising from Innovative	Comment noted.

			Precision Improvement Techniques, which would not be considered GMOs. The legal definition of these latter organisms is based on the following criteria: "I - product with proven absence of recombinant DNA/RNA, obtained by a technique that employs GMOs as a parent; II - product obtained by a technique that uses DNA/RNA that will not multiply in a living cell; III - product obtained by a technique that introduces site-directed mutations, generating gain or loss of gene function, with the proven absence of recombinant DNA/RNA in the product; IV - product obtained by a technique where there is temporary or permanent expression of recombinant DNA/RNA molecules, without the presence or introgression of these molecules in the product; and V - product where techniques are used that employ DNA/RNA molecules that, whether absorbed or not in a systemic way, do not cause permanent modification of the genome". Brazil does not count as yet with a dedicated, specialized regulatory agency to enforce and ensure the effective implementation of Law 11.105/2005 and related statutes.	
Global Industry Coalition	65	39-44	**Revise** for factualness. We question how true the statement "as regulatory authorisation is increasingly being sought" is. Are there references or figures to support this statement? Increased activity is more likely to be developers seeking regulatory clarity from authorities. However, the fact that regulators have been discussing what is the appropriate regulatory approach to genome editing and other technologies, does not imply that such discussions took place under the umbrella of synthetic biology. Perhaps a more accurate statement would be that in addition to consideration on synthetic biology, regulators have been addressing other enabling technologies, including genome editing and others.	Comment noted and Revision made.
JCVI	65	42-44	This statement is misleading. The sentence, and the 2.5 pages that follow, make it appear that the only applications of synthetic biology that have received regulatory review and attention are those that employ genome editing, gene drives, and RNAi technologies. This is by no means true. Most products of synthetic biology are well-covered by current regulatory regimes	Comment noted and Revision made.

			for biotechnology, as briefly covered in section 7.2. The three technologies highlighted in 7.1 are examples of those that have received additional scrutiny.	
Global Industry Coalition	65	46	**Delete** "*wide*"	Editorial suggestion noted and Revision made.
Global Industry Coalition	65	47	**Delete** "*will*"	Editorial suggestion noted and Revision made.
Global Industry Coalition	65	47	**Insert** "*LMO*" prior to "*regulatory purview*".	Editorial suggestion noted.
EBRC	65	Section 7	Recommendation to use same classification (unmanaged-(semi) managed-contained for section 6 biosafety concerns-chapters to enable better category related information and recommendations	Editorial suggestion noted.
New Zealand - CIRB	65-66	46-48	These sentences are internally inconsistent and contradictory. The paragraph begins by saying both that a wide range of positions have been taken (and thus implying that there are a substantial number of countries taking positions) to a sentence or two later saying that almost no countries have declared a position but where they have it is based on just one, the metaphor of a mimic of nature. Either a wide range, or a narrow range, which is it? The loudest voices, and countries with the resources to make their voices loud, have been those who argue some nature equivalence logic. (See comment below related to text on page 86.) In my view the number of countries taking a position has been small and are defined by a narrow spectrum of economic interests and cultural similarities.	Comment noted and Revision made.
JCVI	65-69		Following the comment above, I think reversing the order of sections 7.1 and 7.2 will give readers a more accurate understanding of national regulatory frameworks for synthetic biology.	Comment noted.

EBRC	65-94	19 - Sections 7-9	Recommend the inclusion of a section on the regulation of biotechnology in general, how this has adapted through the last several decades, and how it is likely to continue to adapt to take into account whatever "synthetic biology" is. While nominally this is Sections 7-9, we go from a broad introduction to very specific ethical or regulatory issues and without taking into account the large and evolving regulatory climate surrounding, for example, plant genetic engineering, where we seem to have somehow 'grown' a worldwide green revolution over time (https://ourworldindata.org/famine-mortality-over-the-long-run).	Editorial suggestion noted.
Global Industry Coalition	66	01	**Delete** "*appeared as*" and **replace with** "*are recognised as comparable to"*	Editorial suggestion noted and text revision made.
Global Industry Coalition	66	01-02	**Delete** "*untargeted due to radiation-based or chemical mutagenesis or targeted by the use of transgenesis or genome editing technologies*" and **replace with** *"…. depend in most cases on whether modifications are comparable to that arising via spontaneous processes or introduced with the use of conventional mutagenesis tools such as irradiation of chemical treatment, or comparable to modifications achieved using transgenic approaches"* The intended message in this sentence is unclear; edits are suggested for clarity according to our understanding of the regulatory situation.	Editorial suggestion noted and text revision made.
New Zealand - CIRB	66	01-33	What this paragraph demonstrates is that there is no internally consistent approach being taken by the example countries. Their choices of inclusion or exclusion are case-by-case, as in plants vs animals in the US. The Japanese and Brazilian examples leave the reader unclear as to whether the determinations deregulate all plants or just those two mentioned, one in each country. This also applies to lines 41-47. In short, this paragraph looks contrived to use a variety of disjointed observations to fit a predetermined narrative. I suggest deleting lines 9-33. Same for 41-47. Lines 34-40 are succinct summaries of the facts and the paragraphs p 66 line 48-67 line 10 follow consistently from 34-40.	Editorial suggestions noted. Revision made.

Global Industry Coalition	66	03	**Insert** *"For instance"* before "*those"* in the beginning of the sentence.	Editorial suggestion noted and Revision made.
Global Industry Coalition	66	04	**Delete** "*genes*" and **replace with** *"(or exogenous) DNA*"	Editorial suggestion noted and Revision made.
Global Industry Coalition	66	05-06	**Revise** for factualness. "…existence naturally or through conventional breeding". How can this be an example of "synthetic biology"?	Comment noted and Revision made.
PRRI	66	06-07	The references are dated 2015/2016 after that, other countries have clarified the regulatory process of genome edited products.	Comment noted. Revision made.
New Zealand - CIRB	66	06-08	This section should have more recent references.	Comment noted. Revision made.
Global Industry Coalition	66	08	**Delete** *"most"* and **replace with** *"many"*	Editorial suggestion noted and Revision made.
Global Industry Coalition	66	09	**Delete** "*Therefore, at one end of the range is*" and **replace with** *"The approaches include"*	Editorial suggestion noted.
Global Industry Coalition	66	11	**Insert** *"on the basis that these do not present novel risks*" after "*methods"*	Editorial suggestion noted.
Global Industry Coalition	66	12	**Insert** *"some of*" before "*those"* in the beginning of the sentence. Not all countries that have created exclusions are CP parties (e.g. Australia)	Editorial suggestion noted and Revision made.
New Zealand - CIRB	66	16-17	This line would be strengthened by a reference. It could be (Heinemann et al. 2021) among others.	Comment noted.
EBRC	66	17-19	This approach of exempting organisms from LMO regulations is agreeable. That said, determining the bounds as to what mutations can happen spontaneously may be a tricky grey area. Recommend case-by-case considerations of applications wherein applications that are deemed safe and cover the objectives of the CBD be exempt from LMO regulations.	Comment noted.

Brazilian Bar Association	66	22	There is a growing number of opinions issued by CTNBio exempting from licensing requirements products presented as non-genetically modified. These decisions are not necessarily based on the best science. For the correct application of existing legal tools, as well as the introduction of standards in this regard, it is recommended the establishment of the above-mentioned regulatory agency to lead government action in this field.	Comment noted.
Global Industry Coalition	66	34	**Insert "***Australia*" to the list of countries. (legislative changes to exclude SDN-1 from the scope of GMO regulation have been implemented in Australia)	Editorial suggestion noted and Revision made.
Brazilian Bar Association	66	34-40	Brazil is a Party to the Cartagena Protocol to the CBD, which aims to ensure the safe handling, transport and use of living modified organisms ("LMOs") resulting from modern biotechnology that may have adverse effects on biological diversity and, as a result, on human health. Since the 1980s, the emergence of environmental concerns worldwide and the adoption of several multilateral environmental agreements have resulted in better awareness of environmental challenges in Brazil and prompted the enactment of a robust and rich environmental law framework. This includes, inter alia, Law 9605/1998, governing environmental crimes and contraventions, regulated by Decree 6514/2008. Additionally, the states and, as regards local interests, the municipalities are empowered to issue and implement their own environmental statutes. Within this framework, Brazilian Law 11.105/2005, regulated by the Decree 5.591/2005, governs genetically modified organisms (GMOs), their by-products and related biosafety matters, including research and trade. The 2005 statute represents an overhaul of an earlier law on the topic, building on the experience with its implementation. Law 11.105/2005 provides for safety norms and inspection mechanisms for the construction, cultivation, production, manipulation, transportation, transfer, import, export, storage, research, marketing, environmental release and discharge of GMOs and their by-products. Informed by the principle of precaution, the Law aims to promote scientific	Comment noted.

			development in the biosafety and biotechnology arena and ensure human health and environmental protection. The Law also outlines a dedicated institutional structure for implementation – the National Biosafety Council (CNBS) and the National Biosafety Technical Commission (CTNBio) – the latter under the Ministry of Science and Technology. Other important environmental bodies are the Ministry of Environment, the National Environmental Council and the Brazilian Institute of Environment and Renewable Natural Resources (IBAMA), the environmental body in charge of implementing the National Environmental Policy and related legislation. Moreover, Federal Law 13.123/2015 governs, comprehensively and in detail, access to genetic resources (GH) for scientific research, bioprospecting, and technological development. Under this Law, the Genetic Resources Management Council (CGen) is the principal institution, acting in coordination with other environmental authorities. This is the Brazilian governance framework for biosafety and biosecurity involving GMOs and genetic resources and which may apply to synthetic biology activities.	
Global Industry Coalition	66	37	**Delete** "*e*" from "*especial*"	Editorial suggestion noted.
New Zealand - CIRB	66	40	Please balance the article reference Fritsche, S., Poovaiah, C., MacRae, E., & Thorlby, G. (2018) with the CBD initiated book chapter: Heinemann, J.A., Coray D.S. and Kurenbach, B. GMO Rules and Regulations in New Zealand In GMOs: Implications for Biodiversity Conservation and Ecological Processes. Edited by D.L. Hawksworth and A. Chaurasia. Springer-Nature https://doi.org/10.1007/978-3-030-53183-6	Comment noted.
PRRI	66	45-47	The Brazilian National Technical Biosafety Commission concluded that the gene-edited hornless cows had no presence of foreign DNA and no off target effects and was not assessed as an LMO https://www.in.gov.br/web/guest/materia/-/asset_publisher/Kujrw0TZC2Mb/content/id/48447747/do1-2018-11-05-extrato-deparecer- tecnico-n-6-125-2018-48447599	Comment noted.

			This decision was later updated, details can be found here https://www.in.gov.br/web/dou/-/despacho-de-13-de-junho-de-2019-163601357).	
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	67 f		This section could additionally discuss which regulatory classifications may be relevant to epigenetically modified organisms. These may arise intentionally (e.g. by RdDm) or unintentionally from the application of RNAi techniques (Dalakouras and Papadopoulou, 2020). Dalakouras, Athanasios; Papadopoulou, Kalliope K. (2020): Epigenetic Modifications: An Unexplored Facet of Exogenous RNA Application in Plants. In: Plants (Basel, Switzerland) 9 (6). DOI: 10.3390/plants9060673.	Comment noted.
Global Industry Coalition	67	11	**Insert** *"certain"* before "*genome edited"*.	Comment noted. Revision made.
Max Planck Institute for Terrestrial Microbiology	67	11 ff	The discussion of detection of genome edits reflects a thorough lack of understanding of limitation of such detection methods. For a more balanced and nuanced treatment of the matter, see, for example, Huang, S., Weigel, D., Beachy, R. N., and Li, J. (2016) A proposed regulatory framework for genome-edited crops. Nat. Genet. 48, 109-111 https://doi.org/10.1038/ng.3484.	Comment noted. Revision made.
Global Industry Coalition	67	12	**Revise** for factualness. *"…products therefore, there is no point in having them regulated"* The statement is misleading and misrepresents the discussions on the topic. A more accurate statement would be that because such products are very similar or identical to products developed with conventional tools and methods, the risks are equally comparable and therefore capturing such products under regulation for GMOs may be disproportionate.	Comment noted. Revision made.
ZKBS	67	12-15	The described detection methods do not allow the identification of a mutant plant as a genome-edited plant (see comment above for page 64). The sentence "However, recent advances in detection methodologies, including the adaptation of techniques already in use by laboratories, such as	Comment noted. Revision made.

			quantitative PCR and digital PCR, could facilitate the detection of genome-edited events more readily (Chhalliyil et al., 2020; Peng et al., 2020; Ribarits et al., 2020)" should therefore be deleted.	
Global Industry Coalition	67	12-15	**Delete** *"However…..; (Ribarits et al., 2020)"* This is repetitive of section 6.2.5 and could be deleted here.	Comment noted. Revision made.
EBRC	67	15-16	The idea that advancements in detection methods are "moot" with regards to policy making is disagreeable. If detection methods and descriptions of synthetic biology become more advanced and refined, it allows for more nuance to be applied to said regulations. Science-based approaches can remove subjectivity of determining if synthetic biology was used and the implications of its deployment. As standards for detection and description advance, so too must the regulations.	Comment noted. Revision made.
Imperial College London	67	20-21	Please replace "most are not ready" with "none are ready" for release	Editorial suggestion noted and Revision made.
Global Industry Coalition	67	21	**Delete** *"from"* and **replace with** *"in"*	Editorial suggestion noted and Revision made.
Global Industry Coalition	67	22	**Insert** *"potentially"* before "*has the ability"*.	Editorial suggestion noted and Revision made.
Imperial College London	67	24-25	These gene drives are undergoing a thorough assessment which is driven by the developers. That is why these gene drives are still in the research and development phase and not close to any release as stated in previous sections.	Comment noted.
Global Industry Coalition	67	32	**Insert** *"adequacy of existing approaches to environmental risk assessment"* after "*principle"*. **Insert** "participation of the IPLCs that may be affected through the..." before "obtention" **Insert** "their" before "FPIC"	Editorial suggestion noted.

Outreach Network for Gene Drive Research	67	32-33	The adequacy of existing guidance and methodologies for the risk assessment of gene drives should be included as another area in which concerns have been raised.	Comment noted.
Global Industry Coalition	67	33	**Delete** *"of IPLCs"* Check name spelling in provided reference	Editorial suggestion noted.
Global Industry Coalition	67	35	**Delete** *"the apparent"* and replace with "*claimed*" **Delete** "the" before "regulatory"	Editorial suggestion noted and text revised.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	67	36-38	"others emphasise the potential benefits of gene drive applications and encourage further development and continued laboratory research (Dolezel et al., 2020)." This statement is a direct quote from the report. In the way the sentence is written here, it suggests the authors of Dolezel et al. (2020) are "others" and of this opinion, which is not the case. Consider identifying a direct source for the statement or at least mark the sentence with quotation marks for good scientific practice.	Comment noted and Revision made.
Outreach Network for Gene Drive Research	67	38	It should be noted that the purpose of continued laboratory research is to improve understanding and knowledge of gene drives and their potential risks and benefits.	Comment noted and Revision made.
Global Industry Coalition	67	38	**Insert** *"that enables improved knowledge and understanding of the technology"* after "*laboratory research"*.	Editorial suggestion noted and Revision made.
EBRC	67	43-46	The CBD and its Protocols may serve a vital role in international governance of gene drives and other synthetic biology applications. That said, these lines give one pause that the CBD may advocate for it being the sole body in determining regulations and enforcement of these applications. This would be contrary to other points in the document that no one entity is going to be able to handle global regulation of synthetic biology methods, products, and deployments.	comment noted

Global Industry Coalition	67	43-46	**Revise** for completeness and balance. If this NGO statement ("… *are currently the best home*") is included here, then others should also be included, e.g. the more strongly supported view that there needs to be collaboration between the CBD and other international fora such as the WHO, which has relevant public health expertise and already established procedures that are applicable to mosquitoes containing engineered gene drives.	Comment noted.
Global Industry Coalition	67	44	**Revise** for factualness. "*substantive work*" is used to describe the work on gene drives under the CBD. Proposals have been made, but nothing has started yet.	Comment noted and Revision made.
Western Michigan University	67	44-46	Since gene drive organisms are already currently under the CBD and its Protocols, this statement implies that there is an alternative being advanced or considered. Such alternatives should be described here if they exist, or if not, then this statement seems superfluous and possibly misleading in its implications.	Comment noted.
New Zealand - CIRB	"68 and elsewhere"		Please do not reduce the external use of dsRNA to "sprays". External use can be achieved using a variety of very different mechanisms and this should be acknowledged and explained to avoid oversimplification and ongoing use of semantics to narrow the discussion. For example, uptake of pesticidal dsRNA via roots may not be a spray, but still could result in a variety of different exposure pathways depending on organism, from ingestion by pests to contact by fungi.	Comment noted and Revision made.
Global Industry Coalition	68	01	**Insert** *" LMO"* before *"regulatory"*.	Editorial suggestion noted Revision made.
New Zealand - CIRB	68	01-03	This line would be strengthened by a reference. I suggest (Heinemann 2019) which is already used in other places.	Comment noted and Revision made.
Global Industry Coalition	68	02	**Revise** for factualness. *"…urgent need…"* This is not consistent with the statement on page 60 line 30-33: "Existing plant protection product risk assessment approaches can be reliably	Comment noted and Revision made.

			used to evaluate dsRNA-based products for topical application, with adaptations only required on a case-by-case basis where additional research might be necessary to assess risk (Mezzetti et al., 2020)."	
Brazilian Bar Association	68	03	RN CTNBio 16/2018 outlines guidelines for topical applications based on RNA – it does not classify them as Genetically Modified Organisms (art.1, §3, I to V).	Comment noted.
New Zealand - CIRB	68	05-07	This sentence projects a pre-determined conclusion as if it were a fact. In saying that topical treatments are non-transgenic, the report is implying that this is a settled issue of science. It is not. Instead it draws upon unofficial definitions of what are genes and other genetic material are as held by some. In fact, in two peer reviewed publications, we demonstrate that both the scientific literature and industry patent claims (with included experimental evidence) converge on the heritability of topical RNA treatments both via long lived (hundreds of generations so far) effects from single exposure treatments and RNA-RNA recombination in eukaryotic organisms with stable RNA components of their genome (ie, fungi) (Heinemann 2019; Heinemann and Walker 2019). Both of these publications are known to the AHTEG and are cited elsewhere in the report (although for side points), so it should be possible to balance this paragraph appropriately with the contrasting point of view and extensive evidence for it. The AHTEG cannot ignore away inconvenient science. The key analysis missing in this section is that there is no basis for assessing the risk of topical (spray, ingestion etc) exposures because they violate point one of Annex III of the Protocol: • "An identification of any novel genotypic and phenotypic characteristics associated with the living modified organism that may have adverse effects on biological diversity in the likely potential receiving environment, taking also into account risks to human health;" because by definition many topical applications will not control exposures, particularly to small and ubiquitous organisms that do inherit the modification. This includes fungi and importantly protozoa, many of which are not even yet described.	Comment noted and Revision made.

			The AHTEG should feature this particular issue with no less fairness than it did the gene drive section where exposure analysis is challenged, and in the case of RNA technology, probably impossible in open air use.	
Third World Network	68	6	dsRNAs are explicitly designed to modify genetic activity of exposed organisms, with some effects potentially hereditary, and thus can be considered a genetic modification technique. Industry patents have been filed that claim heritability, as well as proprietary rights over exposed organisms and their offspring. Any proposals to regulate solely the dsRNA product and not the exposed organisms thus fails to acknowledge the biosafety and socioeconomic implications of this new form of genetic modification.	Comment noted and Revision made.
ETC Group	68	06	dsRNAs are explicitly designed to modify genetic activity of exposed organisms, with some effects potentially hereditary, and thus can be considered a genetic modification technique. Industry patents have been filed that claim heritability, as well as proprietary rights over exposed organisms and their offspring. Any proposals to regulate solely the dsRNA product and not the exposed organisms thus fails to acknowledge the biosafety and socioeconomic implications of this new form of genetic modification. The document states that products based on RNA-based technologies could be considered "non-transgenic" (and thus could avoid total or partial biosafety evaluation), when the paper has already acknowledged risks of epigenetic change from the RNA that has been introduced (see note on p.61 Line 24). This needs correcting as, otherwise, the Singh et al. (2019) paper cited risks misleading the reader.	Comment noted and Revision made.
African Centre for Biodiversity	68	6	dsRNAs are explicitly designed to modify genetic activity of exposed organisms, with some effects potentially hereditary, and thus can be considered a genetic modification technique. Industry patents have been filed that claim heritability, as well as proprietary rights over exposed organisms and their offspring. Any proposals to regulate solely the dsRNA product and not the exposed organisms and therefore fails to acknowledge the biosafety and socioeconomic implications of this new form of genetic modification. The document states that products based on RNA-based technologies could	Comment noted and Revision made.

			be considered "non-transgenic" (and thus could avoid total or partial biosafety evaluation), when the paper has already acknowledged risks of epigenetic change from the RNA that has been introduced (see note on p.61 Line 24). This needs correcting as, otherwise, the Singh et al. (2019) paper cited risks misleading the reader.	
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	68	12	Delete one "that"	Revision made.
New Zealand - CIRB	68	14-27	I would also point out that by Australia's decision to exempt a highly defined and limited scope of external treatments of organisms with dsRNA from the GMO regulations, *they had not arrived at the conclusion that treatments do not create genetically modified organisms under regulations*. Indeed, the list of limitations to the exemptions make clear that the technology can produce GMOs, as per the conversion of the RNA into DNA or through direct transfer of viruses or the potential for RNA-RNA recombination of even partial viruses. Therefore, they have made a decision with specific relevance to how to regulate rather than whether to govern. (See comment above related to page 65 lines 20-32). Moreover, this is entirely different to what New Zealand did. Note, that New Zealand recalled that decision and issued a new determination with much more limited scope.	Comments noted.
WHO	68	37	Biological and Toxin Weapons Convention	Comment noted.
Global Industry Coalition	68	47	**Delete** *"their"* and **replace with** "*an enabling"*.	Editorial suggestion noted and revision made.
EBRC	69	12-14	Agree with this emphasis from the National Academies of Sciences Engineering and Medicine. Innovation often outpaces regulatory space. Regulatory systems must be able to rapidly (and appropriately) respond to new technologies in order to enable deployment	Comment noted.

GJSG on SynBio	69	21-30	We support the view that "most synthetic biology approaches result in GMOs that can be assessed according to the existing (national) regulatory frameworks, the applicable European Directives (2001/18/EC and 2009/41/EC), and the Cartagena Protocol."	Comment noted.
EBRC	69	21-30	Important conclusion.	Comment noted.
WHO	69		· See Belgian Biosafety Server (e.g. assessment tools, reporting requirements, best practices, GMOs) – https://www.biosafety.be/ • See Canadian government website -- https://www.canada.ca/en/services/health/biosafety-biosecurity.html • See UK Parliamentary testimony and reports on biosecurity -- https://committees.parliament.uk/work/316/biosecurity-and-national-security/publications/ • WHO Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing – See Human Genome Editing: A DRAFT Framework for Governance (3 July 2020) (https://www.who.int/docs/default-source/ethics/governance-framework-for-human-genome-editing-2ndonlineconsult.pdf?ua=1) E.g. see Box 2: Existing analysis of regulatory status of human genome editing by nos. of countries and nos. of documents according to WHO region [71 countries in total, 80 documents in total] • NIST work streams on standards setting (quality assurance and harmonization) in the biological sector (see https://www.nist.gov/topics/bioscience/nists-role-bioeconomy and https://www.nist.gov/bioscience)	Comment noted.
New Zealand - CIRB	70	01-13	Not toxic genes. Genes that would result in the production of toxins.	Comment noted and Revision made.
Outreach Network for Gene Drive Research	70	10	This is potentially misleading, as gene drive researchers have collectively developed principles for responsible and safe gene drive research, for example: - Emerson C, James S, Littler K, Randazzo F. Principles for gene drive research. Science 358 (6367), 1135-1136 DOI:10.1126/science.aap9026.	Comment noted.

			https://science.sciencemag.org/content/358/6367/1135 - Akbari OS, Bellen HJ, Bier E, et al. Safeguarding gene drive experiments in the laboratory. Science. 2015;349(6251):927-929. doi:10.1126/science.aac7932. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4692367/	
New Zealand - CIRB	70	14-18	This is a particular interpretation of the post Asilomar time. In fact, Asilomar participants had a variety of views (Russell 1975). What is missing in this and later paragraphs is the view of Brenner and others that the essence of the need to regulate was in the ability of gene technologies to allow rapid changes across many dimensional scales. Reported at the time was the fear of some scientific leaders, such as James Watson, Joshua Lederberg and David Baltimore, that without 'self-governance' a hypothetical bureaucracy would imposed governance. As Baltimore said at the time "We have to do what we're doing. Otherwise someone else will come in and do it for us" (Russell 1975). This was not a reflective endorsement of the efficacy of self-governance, but instead as Lederberg put it, an attempt to avoid even guidance because it might become "crystallized into legislation" (Russell 1975).	Comment noted.
CDTBE-UK	70	17	Need a space after the bracket "…2011) involving …"	Editorial suggestions noted and revisions made.
CDTBE-UK	70	17-18	The Asilomar Declaration focused on biosafety, which represents the first level of ethical consideration that should be investigated, before discourse moves onto subjects such as the societal impact of technological deployment. The moratorium was declared upon investigation at this first level, and hence there was no need to discuss the societal impacts at that stage. Further, the authors of the declaration - being largely scientists - were most qualified to provide discourse on the biosafety aspects, rather than social aspects of the technology involved. The ETC group chooses to view the focused nature of the declaration as a product of elitism and conspiracy, an attempt to subvert public involvement in regulation, rather than one that recognised the slow pace of legislature, and the need for fast action in the name of public good.	Comment noted.

			The ETC group refers to the declaration as a "move by a handpicked group of elite scientists to pre-empt government oversight" (ETC Group, 2007), a claim that is conjecture at best, and a wilful attempt to misrepresent and undermine the ethical standing of the synthetic biology community at worst.	
CDTBE-UK	70	31-32	Direct engagement between governments and researchers is of critical importance here, to build a discourse that is both informed by the realities of risk and opportunity, and interpretable enough to be accessible by the public and legislators.	Comment noted.
UN Div. Ocean Affs.	70	36-39	The description of the measures under the London Protocol to the London Convention does not describe accurately the measures adopted thereunder and reflected in Resolutions LC-LP.1 (2008), Resolution LC-LP.2(2010) and Resolution LP.4(8) of 2013.	Revision made.
Global Industry Coalition	70	41	**Revise** for factualness. "*concrete agreements*" What about commitments made and principles developed by the gene drive research community? E.g. : - commitments to the safe and responsible development of gene drive technology - Akbari et al 2015 Science doi: 10.1126/science.aac7932 - guiding principles for gene drive research - Emerson et al 2017 Science doi: 10.1126/science.aap9026	Revision made.
JCVI	70, 71	33-47, 1-12	This section mixes calls for moratoria with discussions of self-regulation. Line 41 (p.70) is clearly contradicted by Lines 13-24 (p.71) and subsections 7.3.3 and subsections 7.3.4. I suggested deleting lines 41-47 (p.70) completely.	Editorial suggestion noted.
Western Michigan University	71	13	These other perspectives should be referenced and not simply mentioned casually.	Comment noted and Revision made.
IWF	71	13	Mention the source and references.	Comment noted and Revision made.

JCVI	71	13-24	This paragraph discussing establishment of community norms is incorrectly included in the subsection on calls for moratoria. This deserves a separate subsection.	Comment noted and Revision made.
EBRC	71	13-24	Important line which raises questions on why the involvement of the science community is so limited? What is proposed to have better engagement?	Comment noted.
Third World Network	71	24	We suggest the addition of this sentence at the end of the paragraph: In fact, given that gene drive applications have the potential to cause serious harm to the environment, which is a public good, it would not be appropriate to place regulation and decision-making about the technology solely in the hands of private actors. Lim, L.C., & Lim, L. L. (2019). Gene Drives: Legal and Regulatory Issues. Third World Network. https://www.twn.my/title2/books/Gene-drives.htm	Comment noted and Revision made.
ETC Group	71	24	We suggest the addition of this sentence at the end of the paragraph: "In fact, given that gene drive applications have the potential to cause serious harm to the environment, which is a public good, it would not be appropriate to place regulation and decision-making about the technology solely in the hands of private actors." Lim, L.C., & Lim, L. L. (2019). Gene Drives: Legal and Regulatory Issues. Third World Network. https://www.twn.my/title2/books/Gene-drives.htm	Comment noted and Revision made.
African Centre for Biodiversity	71	24	We suggest the addition of this sentence at the end of the paragraph: In fact, given that gene drive applications have the potential to cause serious harm to the environment, which is a public good, it would not be appropriate to place regulation and decision-making about the technology solely in the hands of private actors. Lim, L.C., & Lim, L. L. (2019). Gene Drives: Legal and Regulatory Issues. Third World Network. https://www.twn.my/title2/books/Gene-drives.htm	Comment noted and Revision made.
CDTBE-UK	72	02	Does not emphasise the impact that all the teams are causing by coming up with brilliant Synthetic Biology strategies to solve world-wide problems.	Comment noted.

			Some of these projects, if funds are available, could be taken from the lab bench into start-ups seeking a change in our society.	
EBRC	72	02-06	These consortia (e.g. IGSC and EBRC) encourage standard behaviours amongst large numbers of relevant parties, spanning government, academia, and industry. These parties help steer the consortia and show encouraging adoption of norms. These do not replace government and international regulations and oversight, but they can provide solid groundwork from which regulations and oversight can be developed.	Comment noted and Revision made.
New Zealand - CIRB	72	07-37	Is this a paid advertisement? Why doesn't ETC get a nice explanatory endorsement too? What is the purpose of section 7.3.4? If it is an attempt to illustrate spontaneous self-regulation, then it needs to have a research basis where its anticipated risk mitigation tactics have been independently verified and effectiveness thoroughly investigated.	Comment noted and Revision made.
Global Industry Coalition	72	10	**Replace** "*form*" with "*from*"	Comment noted and Revision made.
New Zealand - CIRB	72	13-15	Here is an example of the uncritical nature of this section. It describes a framework that already *endorses* a commercial-technological vision while cementing a view of risk narrowly defined by that described by a certain subset of technical experts (Herrero et al. 2015; Montenegro de Wit 2020; Roberts et al. 2020).	Comment noted.
EBRC	72	34	Importance and impact of IP on investments and actual developments should have more prominent recognition than few lines on p74 3-7. Section 7, especially 7.4 reflects mostly on concerns of the past 20 years that did not materialize, with limited attention for recent developments in the report update period.	Comment noted and Revision made.
Global Industry Coalition	72	38	**Replace** "*biodiversity*" in the section title with "*synthetic biology*"	Editorial suggestion noted and Revision made.

Global Industry Coalition	72		Add a new section "7.3.5 Community Biology Biosafety Handbook" "Another example of self-regulation, specifically in the area of "DIY Bio" can be found in the Community Biology Biosafety Handbook, an open manual that offers biosafety protocols, practices, and recommendations aimed specifically at community biology initiatives. Authored by biosafety experts and formed community lab leaders, the manual includes biological, chemical, and equipment safety, as well as specific citizen science topics such as interview practices for screening potential lab members. Given that biotechnology, synthetic biology and community biology are rapidly evolving, the manual was conceived as a living document, to be edited, updated and expanded by the community members." Reference: Community Biology Biosafety Handbook (Angela Armendariz, Patrick D'Haeseleer, David Gillum, Daniel Grushkin, Eric Harness, Todd Kuiken, Jenny Molloy, Community Biology Biosafety Handbook, Google Docs ed., Genspace & North Carolina State University, 2020 https://www.genspace.org/community-biology-biosafety-handbook)	Editorial suggestion noted and Revision made.
Western Michigan University	73	04	This phrase, "appear to be valid concerns", interjects a value judgment on those concerns, which are inappropriate for this document. I suggest that the document be screened for similar value judgments, which should be eliminated.	Editorial suggestion noted and Revision made.
Global Industry Coalition	73	08	**Edit** *"pro-poor"*. This is not a clear term.	Comment noted and Revision made.
New Zealand - CIRB	73	08-10	This single publication is insufficient to justify the conclusion that regulatory hurdles are the more important barrier to "pro poor" technology. The view is highly contested and there are numerous papers on either side. This paragraph is highly leading. Even the AHTEG does not believe it as they point the finger to IP costs in lines 44-46 as being substantial. However, here all that is being accounted for is patent registration fees. These are the smallest costs of IP. The much larger costs come from defending claims. Therefore, when a true accounting of IP costs is made, it will both undermine the statement in lines 8-10 and dwarf the figure stated in lines 44-46.	Comment noted.

IWF	73	17	There is no such statement that ensure that they are ready or going to be ready for market release.	Comment noted and Revision made.
Western Michigan University	73	17-18	Engineered gene drives are not approaching commercial release.	Revision made.
PRRI	73	17-18	What is meant by approaching commercial release? Next year? Within 5 years? 10 years? The way is written is vague and subject to different interpretations.	Comment noted.
EBRC	74	03-07	This is an important consideration. Companies require some form of IP protection in order to survive and bring technologies to market. More broadly, can both of the models review in section 7.4 coexist? (both IP protection models as well as the BioBrick approach)	Comment noted.
ZKBS	74	18-20	The text should read "including the operational definition developed by the Ad Hoc Technical Expert Group on Synthetic Biology and ~~acknowledged by the Conference of the Parties~~ *considered useful by the Conference of the Parties as a starting point for the purpose of facilitating scientific and technical deliberations under the Convention and its Protocols*;" The operational definition was not acknowledged by COP. Instead, the COP acknowledged that the outcome of the work of the Ad Hoc Technical Expert Group on Synthetic Biology on the operational definition is "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"	Editorial suggestions noted and revisions made.
Global Industry Coalition	74	23-32	**Delete** paragraph after the first sentence. The information in the paragraph is not relevant here - excessive detail.	Editorial suggestion noted.
Global Industry Coalition	74	34-40	Put CBD text in italics here and throughout the document where such text is cited.	Suggestion noted

PRRI	74	38	Synthetic Biology is not a technique but a mindset	Comment noted.
CDTBE-UK	75	01	This is a very important point to consider, and should remain emphasised. However, it is also important to ensure that said procedures emphasise the project-specific nature of said assessment, and ensure that both the procedures and groups utilising them are dissuaded from undue extrapolation to a technology level. Differing implementations of the same technologies might yield significant benefits to biological diversity, through minimising land use and ecological disruption, and assessment procedures should encourage modifications to proposals to embody this kind of approach.	Comment noted.
Global Industry Coalition	75	14	The interpretation of "likely" and "significant" will be decided at national levels according to their circumstances (recall their sovereignty regarding environmental policies - Art2).	Comment noted.
Global Industry Coalition	75	17	**Delete "***negotiation"* and **replace with** "*development"*	Editorial suggestion noted.
Global Industry Coalition	75	21	Put CBD text in italics here and throughout the document where such text is cited.	comment noted
Global Industry Coalition	75	32	**Insert** *"broad"* after "*this"* at the end of the line	Comment noted.
Global Industry Coalition	75	34	**Insert** "*every term used in the definition of biotechnology, or in the obligations set out in Article 8(g), e.g. ...*" after "*define"*	Editorial suggestion noted.
Global Industry Coalition	75	41	**Insert** *"It also depends on whether or not the subsidiary agreement, the Cartagena Protocol on Biosafety to the Convention on Biological Diversity, applies (refer to relevant CP section)."* as a new sentence at the end of the paragraph.	Suggestion is noted.
Global Industry Coalition	75	43	**Insert** after *"organisms"* the text *"... (LMOs) but the definition can be found in the subsidiary agreement, the Cartagena Protocol. There is general agreement that most organisms developed through synthetic biology are*	Suggestion is noted. Revision made.

			LMOs as defined by the Cartagena Protocol". Reference section 8.2.1 and reports of the AHTEG on Synthetic Biology.	
Global Industry Coalition	75	44	**Insert** before "*negotiators*" the text "*in the drafting of the Convention*"	Editorial suggestions noted and revisions made.
Global Industry Coalition	75	44	**Delete** "*replaced the term*" and **replace with** "*chose to use the term LMO instead of*"	Editorial suggestion noted.
Global Industry Coalition	75	45	**Delete** "*to broaden the scope of obligations under the relevant articles (Glowka et al., 1994*)." and **replace with** "*to avoid terms already in use in national legislation. However, the two terms are considered functionally equivalent.*" In practice, the terms are considered functionally equivalent, and this is indicated in the Secretariat FAQs: http://bch.cbd.int/protocol/cpb_faq.shtml#faq3. Also: https://www.biodiversitya-z.org/content/living-modified-organism-lmo	Editorial suggestion noted.
Global Industry Coalition	75	12-14	**Revise** for factualness. This is a general statement that is not supported by "as has been discussed earlier" for "many" applications.	The editorial suggestion is noted and Revision made.
Global Industry Coalition	75	07-09	**Revise for factualness.** **This would only apply if the outcome was not an LMO within the scope of CBD Art8(g) or the Cartagena Protocol.**	Editorial suggestion noted.
Global Industry Coalition	75	14-15	**Revise** for factualness. "…may also have to take into account the case of low-probability, high-impact scenarios which some synthetic biology applications may pose" Is there a credible reference for this statement?	Editorial suggestion noted. Revision made.
Global Industry Coalition	75	30-32	Put CBD text in italics here and throughout the document where such text is cited.	

Global Industry Coalition	75	36-37	**Delete** sentence and **replace with** "*However, it is generally accepted that synthetic biology falls within the CBD definition of "biotechnology", and that Article 8(g) applies*". The reports of the AHTEG on Synthetic Biology should be referenced.	Editorial suggestion noted.
Global Industry Coalition	75	44-45	**Delete "***with "living modified organisms***"**	Editorial suggestion noted.
Global Industry Coalition	75-76	46-47, 1-3	**Delete.** *"Unlike the Cartagena Protocol's definition of living modified organisms, which applies to organisms obtained through the use of modern biotechnology, the Convention's use of the term is meant to include organisms whose genetic material is modified through traditional techniques, such as selective breeding and artificial insemination, as well as "organisms whose genetic material is more directly modified through, for example, recombinant DNA technology" (Glowka et al., 1994).*	Editorial suggestion noted adequate.
Global Industry Coalition	76	07	**Insert** after *"context of"* the text *"Article 8(g) of"*	Editorial suggestion noted.
Global Industry Coalition	76	08	**Replace** "*are*" in "areas of research that *are* considered" with "*may be*"	Revision made
Global Industry Coalition	76	19	**Replace** "*may*" with "*is*"; **delete** "*be*" before relevant	Comment noted.
Global Industry Coalition	76	25	**Insert** "*certain applications of"* before "*synthetic biology*"	Editorial suggestion noted.
Global Industry Coalition	76	32	**Replace** "*have been*" with "*are only*"	Editorial suggestions noted and revisions made.
Global Industry Coalition	76	39	**Delete** *"significantly"* – this is speculative language	Editorial suggestions noted and revisions made.
Global Industry Coalition	76	40	**Delete** *"genome edited animals and plant"* as this is not example of synthetic biology	Editorial suggestions noted and revisions made.

JCVI	76	08-11	This is incorrect and misleading. Most of these areas of research cannot be categorized as "living" vs "non-living". For example, one can engineer a non-living genome, but the reason for doing this is to use it in a living organism. This applies to most of this list. Cell-free systems, however, are non-living.	Revision made.
Global Industry Coalition	76	27-30	**Delete** the text "*One possible interpretation of this text is that two categories of risks are included – risks associated with the use of living modified organisms and risks associated with the release of living modified organisms. The text could also be interpreted to consider only those risks associated with both the use and release of living modified organisms.*" Please note that the text discussing the two possible categories of risk is unnecessarily complicated and confusing things. The "use" itself may be release.	Editorial suggestion noted.
Global Industry Coalition	76	36-38	**Delete** sentence; the examples listed cannot be justified as examples of synthetic biology!	Revision made.
PRRI	76	38-43	Not all these applications are expected to reach market soon, many examples here are under development. It is better to be precise and give specific examples of near market products and they expected availability in years.	Revision made.
Western Michigan University	76	41-42	These are not "near-market ready", if this phrase has the meaning that I think it does.	Revision made.
Global Industry Coalition	77	02	**Insert** "*and the Cartagena Protocol*" after "*8(g)"*	Editorial suggestion noted.
Global Industry Coalition	77	07	**Insert** new text *"Therefore, a country has the right and not an obligation to regulate access to and use of their genetic resources, and ABS obligations will only apply if imposed under national ABS laws and as defined under such laws."*	Editorial suggestion noted.
Global Industry Coalition	77	13	**Insert** new sentence *"Although CBD Art 15 recognises sovereign rights of states and hence the*	Editorial suggestion noted.

			key principle of ABS, the Nagoya Protocol further operationalises these principles and the actual ABS obligations are defined under relevant national law"	
Global Industry Coalition	77	33	**Delete "***units of heredity distinguished genes from "junk" DNA***."** and **replace with** "*…units of heredity contain genes, i.e. distinguished genes "(sequences that encode proteins)" from "junk" DNA "(non-coding sequences)*"	Editorial suggestion noted.
Global Industry Coalition	77	34	**Delete "…***understandings of heredity have changed dramatically; junk DNA is no longer considered "junky," and functional units of heredity may need to be interpreted beyond the gene itself to include, for example, epigenetics which involve functional, and sometimes inherited, changes in the regulation of gene activity and expression that are not dependent on gene sequence (Ganesan, 2018; Gemmell, 2021) and which are increasingly implicated in linking genetics to the environment and disease (Cavalli & Heard, 2019).***"** **and replace with** "…understandings of both heredity and junk DNA have advanced and functional units of heredity may be interpreted beyond the gene itself." while retaining the relevant references from the original text. The text creates confusion regarding the scope of genetic material.	Editorial suggestion noted.
Global Industry Coalition	77	43	**Delete "***types of value –"* **Insert** "value" after "potential"	Revision made.
PRRI	77	44	Since there are no tools and techniques that are exclusively used in Synthetic Biology better to change to Tools and techniques also used in Synthetic Biology.	Editorial suggestion noted.
Global Industry Coalition	77	09-10	**Delete** sentence**.** The statement that this "*would give rise to an obligation*" is not necessarily correct- it depends on what the Party has chosen to implement (recall their sovereignty - line 5). This text (here and in sections immediately above)	Revision made.

			assumes that treaty provisions are directly applied verbatim in parties - this is not the case and is an inaccurate simplification.	
Global Industry Coalition	77	21-22	**Delete "***the access requirements of the Convention would, in general*," and **replace with** "*ABS obligations under national laws might*"	Editorial suggestion noted.
Global Industry Coalition	77	27-28	Put CBD text and definitions in italics here and throughout the document where such text is cited.	Suggestion noted
Global Industry Coalition	77	43-44	**Delete** *"the state of art of technology as well as dynamic"*	Editorial suggestion noted.
EBRC	77	Section 8.1.5	The definition of "genetic material" is unclear as to whether it refers to exact sequences identified in a genome of a given source only, or includes modified sequences (e.g. codon optimization for heterologous gene expression in non-native host). The extent of regulation is dependent on the clarity of this definition. A scenario in which DSI that are variants of source genetic material not be restricted by ABS in the CBD is recommended. Further, inclusion of digital information is considered a major concern, due to lack of transparency (definition of derivatives, origin/uniqueness of digital sequence information in databases), that will lead to confusion, require significant resources both from researchers and regulators and hamper innovation. The isoprene example in section 8.4.3 is interesting in that regard.	Comment- noted.
Global Industry Coalition	78	19	**Insert** *"is currently an active area of discussion under the Convention and the Nagoya Protocol, as well as other international fora concerning genetic resources."* after "*resources*"	Revision made
EBRC	78	24	Though initially opposed to situations where benefit sharing is set up based on the source of a genetic sequence, restricting access to DSI would significantly hamper innovation.	comment noted.
Global Industry Coalition	78	02-04	**Delete** sentence. The ways of capturing value changes, not the genetic resource/material.	Editorial suggestion noted.

Global Industry Coalition	78	10-11	**Delete** *"– from DNA and RNA sequences to amino acid and protein sequences through to biochemical information –"* *This suggests (and could pre-empt) types of digital information however a definition of "digital sequence information" has not been agreed.*	Editorial suggestion noted.
Global Industry Coalition	78	19-38	**Delete** COP process and decisions are not as detailed in other sections of this document, and this information does not provide any clarity on the topic.	Editorial suggestion noted.
Global Industry Coalition	78-79	40-42, 1-25	**Delete** text in section (b) *Genetic resources originating from synthetic biology* Synthetic biology applications may use genetic resources, but the resulting products are not themselves genetic resources. Just because they contain genetic material, they are not a genetic resource in the scope of the CBD/NP. This whole section is confusing and misleading and should be deleted. Alternatively, it should be explicitly stated that synthetic biology products are not genetic resources (this is not "another open question"). Note that synthetic biology applications may use genetic resources, but the resulting products are not themselves genetic resources. Just because they contain genetic material they are not a genetic resource in the scope of the CBD/NP. The products resulting from synthetic biology are man-made and as such are not a genetic resource over which states can claim sovereign rights (how to define a country of origin where these resources can be found in situ – there is no such thing as a country where they have acquired properties through influence of the natural surroundings in which they occur).	Editorial suggestion noted.
Global Industry Coalition	79	28	**Delete** *"pursuant to"* and **replace with** *"in"*	Revision made.
EBRC	79	21-25	These considerations have the potential to become contentious. Defining the limits of ABS for the products from synthetic biology stemming from given genetic resources must be clear. Given the potential complexity, it is recommended that directly involved parties come to agreements where possible.	Comment noted.

Global Industry Coalition	79	27-28	**Delete** *"A number of COP decisions (e.g. COP Decisions XI/29, XII/2 B, XIII/23 B and 14/24) have sought to implement"* and **replace with** *"The Convention includes provisions on..."*	Revision made.
Global Industry Coalition	79	28-29	**Delete** *"of Convention"*	Editorial suggestion noted.
Global Industry Coalition	79	38-41	Put treaty text in italics	
Global Industry Coalition	80	17	**Suggested edits** to place the paragraph into the context of the section. **Delete** "a useful proxy" and replace with "an" **Insert** "activities" after "R&D" **Insert** "around the world." after "synthetic biology" **Delete** "by 2017" **and replace with** "*In the work of Shapira et al (2017), a bibliometric search approach was developed to identify scientific papers published in this domain, and provide insight on patterns of international spread, funding, and disciplinary contributions*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	80	18	**Insert** "*Their approach revealed that...*" before "*more than*"	Editorial suggestions noted and revisions made.
Global Industry Coalition	80	09-10	**Delete** *"holding that Parties shall"* and **replace with** *"obliging Parties to"*	Editorial suggestions noted and revisions made.
Global Industry Coalition	80	10-12	**Put treaty text in italics**	Revision made.
Global Industry Coalition	81	14	This section is missing comment on the Nagoya Protocol and its explicit recognition of traditional knowledge associated with genetic resources.	Editorial suggestions noted.
Global Industry Coalition	81	44	**Insert** *"two"* before *"subsequent meetings"*	Editorial suggestions noted and revisions made.
Global Industry Coalition	82	02	**Insert** "*on the topic of risk assessment and risk management*" at the end of the sentence.	Editorial suggestions noted.

Global Industry Coalition	82	04	**Replace** *"living organisms"* with *"LMOs"*	Editorial suggestion noted.
PRRI	82	Table 1	The table missed the requests for information on Synthetic Biology following the New and Emerging Issue criteria in decision IX/29 in 2010, 2012, 2014, 2016, 2018… and that the analysis did not yet conclude whether Synthetic Biology is a New and Emerging Issue.	The table only contains a summary of the substantive matters and not operational ones. Revision made to clarify that.
ZKBS	82	Table 1	Dec. 13/17 (2016): on the operational definition it must read "~~Acknowledged the operational definition of "synthetic biology" and~~ considered *the operational definition* as a useful as a starting point for the purpose of facilitating scientific and technical deliberations under the Convention and its Protocols." The operational definition was not acknowledged by COP, instead the COP acknowledged that the outcome of the work of the Ad Hoc Technical Expert Group on Synthetic Biology on the operational definition is "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"	Comment noted.
Global Industry Coalition	83	02	Refer to the legal basis for the Cartagena Protocol - Art 19(3) of the Convention.	Revision made.
Global Industry Coalition	83	18	Insert new sentence after "*modern biotechnology."* "*The Cartagena Protocol defines the terms "living organism" (see p 76, lines 4-6) and "modern biotechnology" (p. 85).*" Provide references to these in the text. Given the statement made in the sentence that follows, there needs to be clear direction to the definition of "modern biotechnology".	Editorial suggestions noted.
Global Industry Coalition	83	23	**Replace "***living modified organisms***"** with **"***LMO*" and use this abbreviation consistently throughout	Editorial suggestions noted.

Global Industry Coalition	83	24	**Delete** *"inform the question of whether a synthetic biology organism falls within or outside the Protocol's definition of "living modified organism"* **and replace with "inform this question."**	Editorial suggestions noted.
Global Industry Coalition	83	27	**Replace "***living modified organisms***"** with **"***LMO*" and use this abbreviation consistently throughout	Editorial suggestions noted.
Western Michigan University	83	20-21	Conversely, neither would a modification that resulted from the use of modern biotechnology that was not a novel combination. Thus some results of gene editing would not be considered an LMO under the Cartagena Protocol, nor should it be the subject of further regulations even if they could be made to fit in the category of synthetic biology (depending upon how that term is ultimately defined).	Comment noted
Global Industry Coalition	84	24	Please **delete** "*outstanding questions*" and **replace** with "*questions that may arise*" since these are not outstanding questions.	Editorial suggestion noted.
Global Industry Coalition	84	25	**Delete** "*organisms*" and **replace** with "*LMOs*".	Editorial suggestion noted.
Global Industry Coalition	84	43	**Delete** "*The situation is less clear with regard to DNA and constituent parts*". The situation is not unclear - these are not LMOs.	Editorial suggestion noted
Global Industry Coalition	84	46	**Delete** "*synthetic biology*" and **replace** with "*use in biotechnology*".	Editorial suggestion noted.
Global Industry Coalition	84	03-15	**Replace "***living modified organisms***"** with **"***LMO*" and use this abbreviation consistently throughout	Editorial suggestion noted.
Global Industry Coalition	84	17-20	The information presented is repeating earlier text. Please refer back and shorten this text.	Editorial suggestion noted.
Global Industry Coalition	84	30-31	**Delete "***seem to primarily*". It is clear that the Cartagena Protocol concerns processed materials, all three instances state: "... products thereof, namely, **processed materials** that are of living modified organism origin, containing	Editorial suggestion noted.

			detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology."	
Global Industry Coalition	84	35-41	This paragraph should include comment that the processed products will be subject to other applicable product-based regulatory regimes, e.g. food, chemicals, pharmaceuticals.	Editorial suggestion noted.
PRRI	84	40-41	Products derived from modern biotechnology or synthetic biology such as pharmaceuticals, chemicals, food additives, etc. are covered by other instruments than the Cartagena Protocol on Biosafety.	Comment noted, see sections 9 and 10.
Global Industry Coalition	85	04	**Delete** "*may not*" and **replace** with "*do not*". Such DNA cannot be defined as an LMO.	Editorial suggestion noted. Revision made.
Western Michigan University	85	04-05	It would be instructive to survey Parties to determine whether any of them regulate naked DNA and parts as "living modified organisms". The word "may" in this sentence should probably change to "do".	Editorial suggestion noted. Revision made.
Global Industry Coalition	85	06-10	**Delete** this paragraph. The text above (p 83, line 19) states that the definitions are "intrinsically interlinked", and here they are being separately analysed and applied in a way that expands their scope. A piece of DNA in isolation is not living or able to replicate. This "DNA and constituent parts" section as a whole is unnecessary.	Editorial suggestion noted .
Western Michigan University	85	11	Pursuant to my previous comment, do any countries do so? If not, this sentence should read "all countries" rather than "many countries".	Editorial suggestion noted.
Global Industry Coalition	85	11	**Delete** "*however*".	Editorial suggestions noted and revisions made.
EBRC	85	11-13	Recommendation for this to remain the norm going forward (many countries opting not to apply Cartagena Protocol to naked DNA and constituent parts because they are considered to be components rather than products of LMOs)	Comment noted.

Global Industry Coalition	85	14	This “novel combination” section is (again) considering definitions in isolation.	Editorial suggestion noted.
Global Industry Coalition	85	15	**Delete** “*can result from*” and **replace** with “*is not a defined term, but one interpretation is that it may be ...*". The suggested edition is required as this is only the view of the paper cited. Another view is that "novel combinations" result from recombinant DNA techniques and the resulting integration of recombinant DNA (usually a transgene) and this is often the interpretation under national biosafety regulations. Another view is that a novel combination does not need to be limited to "functional units of heredity". To be more balanced, these alternative views should be presented and should also include the interpretation provided by regulatory bodies in different LATAM countries as part of exclusion of genome editing outcomes from the scope of GMO regulations. Note that these interpretations differ from and supersede the one referenced to Mackenzie 2003.	Editorial suggestions noted and revisions made.
Global Industry Coalition	85	16	Please note that Mackenzie 2003 is not in the reference list.	Revision made.
Global Industry Coalition	85	21	**Delete** *“would*” and **replace** with *“may”.*	Editorial suggestions noted and revisions made.
Global Industry Coalition	85	23	**Delete** *“would likely still*” and **replace** with “*may*”.	Editorial suggestions noted and revisions made.
Global Industry Coalition	85	24	**Delete** “*because*” and **replace** with “*where*”.	Editorial suggestions noted and revisions made.
Global Industry Coalition	85	24	**Delete** “*could*”.	Editorial suggestions noted and revisions made.
Global Industry Coalition	85	44	**Delete** *“may*” and **replace** with *“would”.*	Editorial suggestion noted. Revision made.

Global Industry Coalition	86	15	**Insert** "*of an LMO*" after "*movement*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	86	44	**Delete** "*The Parties*" and **replace** with "*Ad Hoc Technical Expert Groups on Risk Assessment"*. The Parties have never endorsed or adopted what the AHTEGs developed.	Revision made
New Zealand - CIRB	86	01-04	*It is more than* "modifications that would not otherwise naturally arise". The point is that they would not occur in nature without the assistance of the technology to design, create and *amplify them to a scale that can cause harm*. For something to occur in nature requires **more than mutation**. Despite the genetic deterministic fantasies of X-men and Superman, mutation is not evolution. What occurs in nature requires both mutagenesis to provide variation, and natural selection (in the case of humans, technology) to act on the variation to increase the proportion of some genotypes relative to others. It does not matter for a governance framework whether or not a dangerous phenotype could be caused by the same mutation occurring spontaneously (naturally arise) or through gene technology if the former was never fit enough to increase to numbers that caused harm (Heinemann et al. 2021). This mistake of failing to differentiate between mutagenesis and evolution as the baseline metaphor is being made with frightening frequency. In fact, it is occurring so often it could be said to be evolving.	Comment noted. Revision made.
Global Industry Coalition	87	08	**Replace** "*living organisms*" with "*LMOs*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	87	11	**Delete** the two sentences starting from "*In addition…*" This example is an LMO, there are transgenic examples of this. There is no reason why Annex III cannot still apply.	Editorial suggestion noted.
Global Industry Coalition	87	24	**Delete** "*more recently in*" and replace with "*For LMOs developed through synthetic biology, questions have been raised concerning the ongoing applicability of the Cartagena Protocol's risk assessment procedures. These questions have focused on challenges with the long-established comparator*	Editorial suggestions noted. Revision made.

			approach, and knowledge gaps regarding assessment of ecological impacts where the application is unprecedented."	
Global Industry Coalition	87	35	**Replace "***living modified organisms*" with "LMOs".	Editorial suggestions noted and Revision made.
Global Industry Coalition	87	36	**Delete** "*with a view to enabling the Subsidiary Body to*" and **replace** with "*who will then*".	Editorial suggestions noted and Revision made.
Global Industry Coalition	87	40	**Delete** "*were still to be held*" and **replace** with "*are in progress (Feb 2021, May-Jul 2021)*".	Editorial suggestions noted and Revision made.
Global Industry Coalition	87	25-26	**Delete** *"recognised the divergence in views among Parties on whether or not additional guidance on specific topics of risk assessment is needed. The COP-MOP".*	Editorial suggestions noted and Revision made.
Global Industry Coalition	87	08-30	**Delete** "*establish a process for the identification and prioritisation of specific issues regarding risk assessment of LMOs with a view to developing further guidance on risk assessment on the specific issues identified, and to*".	Editorial suggestions noted and Revision made.
Global Industry Coalition	87	31-32	**Delete "***and living modified fish".*	Editorial suggestions noted and Revision made.
Western Michigan University	87	38-40	This sentence will now have to be revised.	Editorial suggestions noted and Revision made.
Global Industry Coalition	87	16-23	**Delete** this paragraph. There is a lot of unnecessary detail here.	Editorial suggestions noted and revisions made.
Global Industry Coalition	87	46	**Insert** "*as described in the section above" after* "*assessment*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	88	03	**Replace** "*Advance Informed Agreement*" with "*AIA*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	88	15	**Delete** "*also left*"	Editorial suggestions noted and revisions made.

Global Industry Coalition	88	20	**Delete** "*At least three*"	Editorial suggestions noted. Revision made.
Global Industry Coalition	88	21	**Delete** "*First*"	Editorial suggestions noted and revisions made.
Imperial College London	88	23	That may be case specific, but not generic to all synthetic biology techniques	Editorial suggestions noted.
Global Industry Coalition	88	23	**Insert** "*certain*" before "*organisms*"	Editorial suggestions noted.
Global Industry Coalition	88	24	**Insert** new text "*This call for containment strategies for organisms resulting from synthetic biology techniques that are different to those applied for LMOs however is questionable. This is because, in line with Article 18 of the Protocol, containment practices (i.e. risk management and mitigation) are based on a risk assessment and, as such, are tailored to minimize the risk to biodiversity and human health*".	Editorial suggestions noted.
PRRI	88	20-23	Considering the wide range of potential products derived from Synthetic Biology the need and level for containment will vary considerably, such an overgeneralized argument from the civil society "… that containment facilities that parties consider to effectively contain LMOs may be unsuitable to contain organisms resulting from synthetic biology" is vague. It would be useful to add in which cases and ways these facilities would not be suitable with the suitable references.	Editorial suggestions noted. Revision made.
Global Industry Coalition	88	24-25	**Delete** the sentence "*Importing countries may need advance information in order to "judge the effectiveness of available containment (Ibid)"*	Editorial suggestions noted and revision made.
Global Industry Coalition	88	27-31	**Revise for completeness. Several edits are recommended, resulting in the following rewrite of the paragraph:** **"EcoNexus, a European civil society group, does not consider DIYbio (do-it-yourself biology)/citizen science individuals and collectives as being able to provide for "contained use" and is concerned that AIA "might**	Editorial suggestions noted and revision made.

			become close to impossible" in such instances (EcoNexus, 2011). Conversely, different reports on DIYbio found that few DIYers are using "sophisticated" synthetic biology, and most work in labs that are rated as Biological Safety Level 1, in a transparent and responsible manner (Grushkin et al., 2013; Landrain et al., 2013; Seyfried et al., 2014; Kuiken, 2016). Several developments involving self-regulation by the scientific community which are relevant to the DIYbio discussion are considered in Section 7.3" **Added reference: Kuiken (2016). Governance: Learn from DIY biologists https://www.nature.com/articles/531167a/**	
Global Industry Coalition	88, 89	20-43, 1-10	**General comment** – the majority of the text in the "contained use" section is devoted to describing issues or concerns raised by certain interest groups. There needs to a be more balanced review of the subject that also reflects established practices for biosafety under containment. We make specific editing recommendations to address this. We also note that the same issues are raised in the Technical Series document of 2015 – therefore, this text is not an "update"	Revision made.
Global Industry Coalition	89	01-10	**Delete** this paragraph. This is not relevant to synthetic biology. If any part of the paragraph is retained, it should be limited to the final three lines: "*Concerns have been expressed that diverging regulatory or ethical ….*".	Editorial suggestions noted and Revision made.
Third World Network	89	01-10	We suggest additional discussion on the lack of international contained use regulations or standards. This is a major gap, especially because of the potential for unintentional releases of synthetic biology organisms, in particular organisms containing engineered gene drives, that might result in transboundary movement or the crossing of national borders, requiring an international response. Additionally, the necessary oversight of laboratory research is presently piecemeal. Complementary national level action, such as requiring the licensing of experiments with organisms containing engineered gene drives in	Editorial suggestions noted. Revision made.

			contained use, would allow for appropriate oversight by the government agencies concerned. Lim, L.C., & Lim, L. L. (2019). Gene Drives: Legal and Regulatory Issues. Third World Network. https://www.twn.my/title2/books/Gene-drives.htm	
African Centre for Biodiversity	89	01-10	The lack of international contained use regulations or standards is a major gap, and requires additional discussion, particularly due to the potential for unintentional releases of synthetic biology organisms, in particular organisms containing engineered gene drives, that might result in transboundary movement or the crossing of national borders, requiring an international response. Additionally, the necessary oversight of laboratory research is presently piecemeal. Complementary national level action, such as requiring the licensing of experiments with organisms containing engineered gene drives in contained use, would allow for appropriate oversight by the government agencies concerned. Lim, L.C., & Lim, L. L. (2019). Gene Drives: Legal and Regulatory Issues. Third World Network. https://www.twn.my/title2/books/Gene-drives.htm	Revision made.
ZKBS	89	29-32	The SARS-CoV-2 vaccines developed so far are not an issue of synthetic biology, but of classical and contemporary genetic engineering (reference Forni & Mantovani 2021). This statement has to be corrected or rather, the sentence should be deleted.	Comment noted
Global Industry Coalition	90	01-03	**Delete** these lines, they are incorrect - their use as pharmaceuticals will be highly regulated ("addressed"). They will **also** be regulated as LMOs. There will be more than one regulatory agency with responsibility.	Editorial suggestions noted and revisions made.
PRRI	90	01-04	No products derived from Synthetic Biology used as pharmaceutical for humans (e.g. vaccines) that fall outside the definition of LMOs were singled-out. These LMOs are exempted from the Cartagena Protocol as they are covered by other relevant agreements.	Revision made.

JCVI	90	01-05	The notion that vaccines and biologics are not "addressed by other international agreements or organizations" strikes me as very odd. World Health Organization, International Council for Harmonization, and many other international bodies address pharmaceuticals, including vaccines and biologics.	Revision made.
Western Michigan University	90	01-05	The meaning of these sentences is unclear. Are there no international bodies that address pharmaceuticals? Currently recombinant DNA-based vaccines (such as those used by Johnson and Johnson or AstraZeneca to develop COVID19 vaccines) are not within the scope of the Cartagena Protocol as far as I know.	Revision made.
IWF	90	03	The sentence needs to be re-written to make clearer sense of the information	Revision made.
Global Industry Coalition	90	26	**Delete** "*to*" and **replace** with "*may*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	90	30	**Insert** "the" before "*potential*".	Editorial suggestion noted. Revision made.
Global Industry Coalition	90	32	**Insert** *", in accordance with a risk assessment (Article 15)."* after "*health*".	Editorial suggestions noted and Revision made..
Global Industry Coalition	90	32	**Delete** "*addresses the extent to which Parties are entitled*" and **replace** with "*provides for Parties*". Article 26 does not specify the "extent", it just states that Parties "may ..., consistent with their international obligations".	Editorial suggestions noted. Revision made.
Global Industry Coalition	90	34	**Insert** "*should they choose to, and consistent with their other international obligations*" after "*IPLCs*".	Editorial suggestions noted and Revision made.
Global Industry Coalition	91	33	**Insert** "*(Article 1 - Supplementary Protocol)*" after "*organisms*" at the end of the sentence.	Editorial suggestions noted and revisions made.

Global Industry Coalition	91	37	**Insert** "*With respect to intentional transboundary movements,"* prior to "*It applies*".	Editorial suggestions noted and revision made.
Global Industry Coalition	92	30	**Insert** *", which are LMOs in the scope of the Cartagena Protocol,"* after "*gene drives*".	Editorial suggestions noted and revision made.
Global Industry Coalition	92	30	**Delete** "*the*" prior to "*environment*".	Editorial suggestions noted and Revision made.
Global Industry Coalition	92	25-29	**Delete** "*Further, as described in Section 4 of this document, it is possible that LMOs resulting from synthetic biology techniques could cause adverse effects on the conservation and sustainable use of biological diversity. For example, unintentionally released organisms may transfer the inserted genetic material and thus change biodiversity at a genetic level, intentionally released organisms may become invasive due to engineered fitness advantages.*" and **insert** *", and require assessment of their potential adverse effects on biological diversity. Concerns associated with these LMOs, as for LMOs that have preceded them, include gene flow and increased invasiveness and persistence."* directly after "*Protocol*". This suggested edit uses more neutral (less presumptive) language.	Editorial suggestions noted and Revision made.
Global Industry Coalition	92	30-31	**Delete** "*of such organisms*".	Editorial suggestions noted and Revision made.
Global Industry Coalition	92	32-34	**Delete** "*As has been discussed, there appears to be significant controversy as to the scope and therefore "significance" of the potential damages. The applicability of the provisions of the Supplementary Protocol would have to be assessed for particular cases*" and **replace** with "*The implications, in terms of determinations of "damage" according to the provisions of the Supplementary Protocol, and its measurability and significance, have not yet been extensively examined*." The suggested edit uses more neutral language because the "controversy" in this context is overstated.	Editorial suggestions noted and Revision made.

Global Industry Coalition	93	04	**Delete** "*addresses the use of terms in the Protocol. It*"	Editorial suggestions noted.
Global Industry Coalition	93	05	**Delete** "*s*" from "*Articles*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	93	06	**Delete** "*It*" and **replace** with **"***Additionally, the Nagoya Protocol*".	Editorial suggestions noted.
Global Industry Coalition	93	18	**Delete "***synthetic biology*" and **replace** with "*genome editing*".	Editorial suggestions noted.
Global Industry Coalition	93	19	**Delete "***food and feed*" and **replace** with "*crops*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	93	19	**Insert "***being examined, are...*" prior to "*under*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	93	19	**Delete** "*advance*".	Editorial suggestions noted and revisions made.
Western Michigan University	93	20	The example is described in 3.3.1(d) rather than Section 3.2?	Editorial suggestions noted. Revision made.
Global Industry Coalition	93	20	**Insert** "*Using the example of sugarcane, ….*" prior to "*If*".	Editorial suggestions noted and Revision made.
Global Industry Coalition	93	20	**Delete "***of sugarcane*" after "*this use*".	Editorial suggestions noted and Revision made.
Global Industry Coalition	93	21	**Insert** "*on its genetic and biochemical composition*" after "*research*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	93	23	**Delete "***interpreted as*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	93	24	**Delete** "*would*" and **replace** with "*may*". This would depend on the requirements of the provider.	Editorial suggestions noted.

Global Industry Coalition	93	24	**Delete** "*and*" and **replace** with "*where*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	93	25	**Replace** "*implementing*" with "*implement*" **Delete** "*obligations*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	93	37	**Insert** *"This is facilitated, where applicable, through the use of mutually agreed terms that include terms on subsequent third-party use (Article 6(g)(iii) - Nagoya Protocol.*" at the end of the paragraph after "*(Ahrén et al., 2012)*".	Editorial suggestions noted.
Global Industry Coalition	93	04-12	Put treaty text in italics.	Suggestion noted
Global Industry Coalition	93	32-33	**Delete "***The use of these synthetic biology techniques raises questions as regards to until what extent the results of modifications of a natural genetic resource continue to be subject to the benefit-sharing obligations."* and **replace** with "*While not unique to synthetic biology, a question that arises is the extent to which a genetic resource continues to be subject to benefit sharing obligations, particularly where it undergoes multiple (subsequent) applications and modifications.*"	Editorial suggestions noted and revisions made.
Global Industry Coalition	93	35-36	**Delete** "*It also provides that "such sharing shall be upon mutually agreed terms".*	Editorial suggestions noted.
Global Industry Coalition	94	02	Refer to where the definition of derivative is provided above instead of repeating it here.	Editorial suggestions noted. Revision made.
Global Industry Coalition	94	13	**Insert** "*However, the synthetically produced enzyme is not the "naturally occurring" biochemical compound per the definition."* at the end of the paragraph after "*(Erickson et al., 2011)*".	Editorial suggestions noted.
Global Industry Coalition	94	25	**Insert "***derivatives, and"* prior to "*access*".	Editorial suggestions noted.

Global Industry Coalition	94	25	**Insert** *"any*" prior to "*benefit-sharing*".	Editorial suggestions noted.
Global Industry Coalition	94	25	**Delete "***in relation to derivatives*".	Editorial suggestions noted.
Global Industry Coalition	94	27	**Delete "***until which extent of*" and **replace** with "*where in..".*	Editorial suggestions noted and text changed
Global Industry Coalition	94	29	**Insert** *", where applicable..."* after "*derivatives*".	Editorial suggestions noted.
Global Industry Coalition	94	36	**Insert** "*the scope of*" after "*beyond*".	Editorial suggestions noted. Revision made.
Global Industry Coalition	94	37	**Insert** new sentence "*It is also recognised that more than one international instrument may be relevant, and consequently there can be multiple national laws and regulations, and overlapping legal responsibilities at national levels.*" prior to "*This*".	Editorial suggestions noted. Revision made.
Global Industry Coalition	94	15-18	**Delete** the sentence. "*A separate question might be whether access to derivatives of organisms resulting from synthetic biology techniques – such as isoprene – would also be covered by the Nagoya Protocol (see similar discussion on access to genetic resources originating from synthetic biology in Section 8.1.5.)*". This is confusing scope and is misleading.	Editorial suggestions noted. Revision made.
Global Industry Coalition	94	19-23	Move this paragraph up to line 7 and attach it to the 2nd paragraph.	Editorial suggestions noted.
Global Industry Coalition	95	08	**Insert** "*Table 2 below*" prior to "*prioritises*".	Editorial suggestions noted. Revision made.
Global Industry Coalition	95	15	**Delete** "*related to the work of the CBD*" as not all examples are related to the CBD.	Editorial suggestions noted. Revision made.
UN Div. Ocean Affs.	95	15	Change "proposed agreement for marine biodiversity beyond national jurisdiction" to "International legally binding instrument under the United Nations Convention on the Law of the Sea on the conservation and	Editorial suggestions noted and revisions made.

			sustainable use of marine biological diversity of areas beyond national jurisdiction under development"	
Global Industry Coalition	95	07-08	**Delete** "*Limited analysis is available concerning potential gaps in international governance. Additionally, this update*". This very topic has been discussed extensively in the synthetic biology work programs of the CBD which implies that extensive analysis is available.	Editorial suggestions noted. Revision made.
Western Michigan University	96	04	This section is missing two key WHO documents, both mentioning gene drives, with the 2021 edition updated to take into account developments in the area of gene drive research: World Health Organization. Guidance Framework for Testing of Genetically Modified Mosquitoes. Geneva: World Health Organization, 2014. World Health Organization. Guidance Framework for Testing Genetically Modified Mosquitoes, Second Edition. Geneva: World Health Organization, 2021.	Revision made.
Outreach Network for Gene Drive Research	96	04	Section 9.2.1. omits WHO's *Guidance framework for testing genetically modified mosquitoes* which is relevant to synthetic biology and should be referenced: Guidance framework for testing genetically modified mosquitoes, second edition. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/publications/i/item/9789240025233	Revision made.
Global Industry Coalition	96	04	This section should refer to the following documents: World Health Organization. Guidance Framework for Testing of Genetically Modified Mosquitoes. Geneva: World Health Organization, 2014. World Health Organization. Guidance Framework for Testing Genetically Modified Mosquitoes, Second Edition. Geneva: World Health Organization, 2021.	Revision made.
Global Industry Coalition	98	14-21	The WHO/TDR and FNIH foundational *Guidance Framework for Testing Genetically Modified Mosquitoes* of 2014, and the 2021 second edition that also includes gene drives should be included here.	Revision made.

WHO	96	13	Delete "a range" – these words appear twice	Editorial suggestions noted and revisions made.
Global Industry Coalition	96	17	**Insert** "*laboratory*" after "*a*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	96	14-15	**Delete** "*which were not intended to be mutually exclusive*".	Editorial suggestions noted and revisions made.
WHO	96	20-21	Replace these lines with the following text: In 2020, the WHO organized three dialogues on dual use research of concern with academies, councils, science editors and publishers and research donors to discuss and learn about current activities and challenges in this area. Since the beginning of 2021, the WHO is developing a Global Guidance Framework for the Responsible Use of Life Sciences with a view to updating guidance in this area of work, particular in light of advances in the life sciences since 2010. The Framework will be aimed at providing Member States and other stakeholders with options to promote the responsible use of the life sciences and to protect against the potential risks caused by accidents and misuse.	Editorial suggestions noted and revisions made.
Global Industry Coalition	99	17	The information in this part is relevant to the section on contained use and it should be mentioned there, and that section referred to here.	Editorial suggestions noted and revisions made.
Global Industry Coalition	99	21	**Insert** "*in a laboratory (i.e. contained use) setting*" at the end of the sentence after "*trends in biosafety*".	Comment noted.
Global Industry Coalition	99	21	**Insert** "*Although focusing on human heath aspects primarily*," prior to "*The Laboratory Biosafety Manual...*"	Comment noted
Global Industry Coalition	99	24	**Delete** "*the third edition*" with "*previous editions*".	Comment noted

Global Industry Coalition	99	25	**Replace** "*The WHO asserts*" with "*It reinforces the idea*".	Editorial suggestions noted.
Global Industry Coalition	99	27	**Replace** "*will allow*" with "*allows for*"	Editorial suggestions noted and revisions made.
Global Industry Coalition	99	32	**Delete** "*synthetic biology,*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	99	26-27	**Replace** "*and that this novel*" with "*Further, such*"	Editorial suggestions noted.
Global Industry Coalition	99	35-37	**Delete** the sentence "*However, countries … life science research*" and replace with "*In that same section, the WHO also advises to not focus on any one of these emerging technologies but rather use one framework in which risks can be assessed and managed regardless of the technology involved*" This is more relevant content to include, as it advocates for a holistic approach using the already available frameworks (instead of additional separate legislation/processes etc.).	Editorial suggestions noted. Revision made.
Global Industry Coalition	100	13	**Delete** ". *It*" after "*Member States*" and **replace** with "*and it*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	100	14	**Delete** "*when it was unanimously adopted by the Sixty-fourth World Health Assembly*". This was already stated on line 3.	Editorial suggestions noted and revisions made.
Western Michigan University	100	03-14	Redundancies in these two paragraphs need to be resolved.	Editorial suggestions noted and revisions made.
Global Industry Coalition	100	03-14	**Revise** to remove duplicated text. The paragraphs should be merged to remove duplicated text.	Editorial suggestions noted and revisions made.
Global Industry Coalition	100	08-09	**Delete** the first sentence of the paragraph as it repeats lines 4-5.	Editorial suggestions noted and revisions made.

Global Industry Coalition	102	30	**Insert "conservation" prior to "challenges".**	Editorial suggestions noted and revisions made.
Global Industry Coalition	104	13	**Insert** "*do not*" prior to "*determine*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	106	07	**Insert** "*environmental*" prior to "*impacts*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	106	15	**Delete** "*either*" and "*pest*"	Editorial suggestions noted and revisions made.
Global Industry Coalition	106	26	**Insert** "*, however the definitions of the Supplementary Protocol (refer to section) provide guidance in the context of LMOs."* after "*damage*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	106	32	**Insert** "*In the Supplementary Protocol, a causal link is required between the damage and the LMO (Article 4)."* after "*species*".	Editorial suggestions noted and revisions made
Global Industry Coalition	106	12-15	Delete "*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*" These are not examples of synthetic biology.	Editorial suggestions noted. Revision made.
Global Industry Coalition	106	08-12	Delete "*through economic, social, and cultural impacts. For example, as considered in Section 4.1. above, depending on the engineered gene drive system, theoretically, a genetic modification could spread through target populations (non-localised) and persist indefinitely (self-sustaining), or be restricted in spread (localised) or persistence (self-limiting). Direct impacts on the transboundary environment, however, would depend on the specific application of synthetic biology*.". The "example" is not about this, and the section is about the environment.	Editorial suggestions noted. Revision made.

Imperial College London	106	11-12	Reference Alphey et al., 2020. Alphey LS, Crisanti A, Randazzo FF, Akbari OS. Opinion: Standardizing the definition of gene drive. *Proc Natl Acad Sci U S A*. 2020;117(49):30864-30867. doi:10.1073/pnas.2020417117	Editorial suggestions noted.
Imperial College London	106	14-15	Importantly, these released self-limiting engineered insects do not contain gene drive constructs.	Editorial suggestions noted. Revision made.
Global Industry Coalition	106	36-37	It is misleading to state that required measures are not clear – for synthetic biology, the measures are codified in CBD Article 8(g) and the Cartagena Protocol.	Editorial suggestions noted. Revision made.
Global Industry Coalition	107	26	**Insert** "*reflecting different levels of acceptance of risk***"** after "*assessed*".	Editorial suggestions noted
Global Industry Coalition	107	28	**Insert** "*compared to existing LMOs and applications of biotechnology*" after "*novel risks*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	107	28	**Delete** "*knowledge*" and **replace** with "*accumulated knowledge and expertise*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	107	07-08	**Delete** "*in particular potential impacts of very low probability but very high magnitude.*".	Editorial suggestions noted.
EBRC	107	27-29	Agree with this opinion. Now, 10 years later, with a multitude of synthetic biology projects this opinion on safety risks and governance is still valid.	comment is noted.
Global Industry Coalition	108	04	**Insert** *"those that are of"* before *"low probability"* **Replace** "and" before "high-consequence" with "but potentially"	Editorial suggestions noted and revisions made.
Global Industry Coalition	108	25	**Insert** *"the notion of"* before *"precaution"*	Editorial suggestions noted.
WHO	109	30	Biological and Toxin Weapons Convention	Editorial suggestions noted.
WHO	110	07	Biological and Toxin Weapons Convention	Editorial suggestion noted.

Max Planck Institute for Terrestrial Microbiology	109	85 ff	"potential impacts of very low probability but very high magnitude". This statement is so broad that it is very difficult to discuss properly. Such considerations make sense to discuss only when evaluating a specific, pre-defined, concrete risk situation.	Comment noted.
WHO	109		Perhaps add text on proposals for science advice function or body to be considered by the forthcoming Review Conference	Comment noted
WHO	110	15	"**Goldblast**" should read "**Goldblat**" [Rotblat and Goldblat both produced useful items. I would propose to include points + reference to Jonathan Tucker's final book (Innovation, Dual Use, and Security: Managing Risks of Emerging Biological and Chemical Technologies, MIT press, 2012)	Editorial suggestions noted. Revision made.
WHO	110		Perhaps add text on BWC prohibitions	Revision made.
WHO	110		2020-2021 outputs of the BWC MSPs and MXs (virtual events) could be checked to update the developments in the current draft report.	Revision made.
PRRI	111	15-17	Please cite references of the use of synthetic biology in climate and weather modification	Editorial suggestions noted.
Global Industry Coalition	112	26	**Replace** *"synthetic biology "*with *"genome editing"*	Editorial suggestions noted.
Global Industry Coalition	112	27	**Replace** *"as is"* with *"and this includes"*	Editorial suggestions noted and revisions made.
Global Industry Coalition	112	21-23	**Delete** *"which defines genetic resources as genetic material of actual or potential value, and genetic material as any material of plant, animal, microbial or other origin containing functional units of heredity"* This information has been provided already several times.	Editorial suggestions noted. Revision made.
UN Div. Ocean Affs.	114	31	Change "157 Parties" to "168 Parties"	Editorial suggestions noted and revisions made.

Global Industry Coalition	114	36	**Delete** *"existing"*	Editorial suggestions noted and revisions made.
UN Div. Ocean Affs.	114	39	Change "to consider" to "to elaborate". Rationale: This is more in line with the mandate of the Conference as reflected in GA resolution 72/249.	Editorial suggestions noted and revisions made.
UN Div. Ocean Affs.	114	40	After "ABNJ", add "with a view to developing the instrument as soon as possible." Rationale: This is more in line with the mandate of the Conference as reflected in GA resolution 72/249.	Editorial suggestions noted and revisions made.
UN Div. Ocean Affs.	114	27-28	Change to "International legally binding instrument under the United Nations Convention on the Law of the Sea on the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction under development"	Editorial suggestions noted and revisions made.
UN Div. Ocean Affs.	114	32-35	The description in this paragraph is inaccurate. Resolution 69/292 of the United Nations General Assembly "stress[ed] the need for the comprehensive global regime to better address the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction". This indicates that, in the view of the General Assembly, there is already a comprehensive global regime in place but this regime must better address those issues.	Editorial suggestions noted and revisions made.
UN Div. Ocean Affs.	114-15	41 (p114), 13 (p115)	The paragraph contains several inaccuracies concerning the process and issues under discussion by the Conference. It is suggested that it be replaced in its entirety by the following: " Marine genetic resources, including the sharing of benefits, have been central to the discussions of the Conference, which is addressing the topics identified in the package agreed in 2011, namely the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction, in particular, together and as a whole, marine genetic resources, including questions on the sharing of benefits, measures such as area-based management tools, including marine protected areas, environmental impact assessments and capacity-building and the	Editorial suggestions noted and revisions made.

			transfer of marine technology. The first session of the Conference was convened in 2018 and the second and third sessions in 2019. At the third session, delegations begun text-based negotiations on the basis of a draft text of an agreement developed by the President of the Conference (A/CONF.232/2019/6). The fourth session of the Conference, which was scheduled to be held in August 2021 pursuant to General Assembly resolution 75/239, was further postponed by the General Assembly to the earliest possible available date in 2022, preferably during the first half of the year. It will consider a revised draft text of an agreement (A/CONF.232/2020/3). Part II of the Revised draft text is entirely dedicated to marine genetic resources, including questions on the sharing of benefits, and contains provisions on, inter alia, access to marine genetic resources of areas beyond national jurisdiction, access to traditional knowledge of indigenous peoples and local communities associated with marine genetic resources of areas beyond national jurisdiction, sharing of benefits, including modalities for such sharing, and monitoring."	
Global Industry Coalition	115	05	**Replace** *"particularly"* with *"including"*	Editorial suggestions noted. Revision made.
Global Industry Coalition	115	07	**Replace** *"modalities for access and benefit sharing"* with *"marine genetic resources, including questions on the sharing of benefits."* The suggested edit is the draft treaty section title.	Editorial suggestions noted. Revision made.
Global Industry Coalition	115	09	**Delete** *"modalities for"*	Editorial suggestions noted. Revision made.
Global Industry Coalition	115	34	**Insert** *"traditional knowledge associated with"* before *"GRs"*	Editorial suggestions noted
Global Industry Coalition	116	22	**Insert** *"in their national regimes"* before *"for"* at be beginning of the line	Editorial suggestions noted and revisions made.
Global Industry Coalition	116	38	**Replace** *"applying them"* with *"defining them at the national level"*	Editorial suggestions noted and revisions made.

Global Industry Coalition	116	21-30	Please **edit** text to reflect that patents are also very relevant to the enabling technologies and tools.	Revision made.
Global Industry Coalition	117	11	**Delete** *"In particular"*	Editorial suggestions noted and revisions made.
Global Industry Coalition	117	23	**Insert** *"potentially"* before *"be excluded"*	Editorial suggestions noted and revisions made.
Global Industry Coalition	117	10-11	**Replace** first sentence with *"Enabling technologies and tools, components, organisms, and products resulting from synthetic biology techniques may fulfil the necessary criteria and may be the subject of patents in one or more jurisdictions"*	Editorial suggestions noted and revisions made.
Global Industry Coalition	118	32-36	**Combine** under one bullet point text beginning with "*defined by the expression*…." and finishing with "*...propagated unchanged*"	Editorial suggestions noted and revisions made.
Global Industry Coalition	121	31	**Delete** "*of*".	Editorial suggestions noted and revisions made.
IWF	121	32	The sentence needs to be re-written to make clearer sense of the information	Editorial suggestions noted. Revision made.
Global Industry Coalition	121	32	**Replace** "*leading*" with "*may lead to*"	Editorial suggestions noted and revisions made.
Global Industry Coalition	121	34	**Insert** a full stop after "*DNA*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	121	40	**Provide** fuller reference, it is not clear that this is referring to the 2015 synthetic biology technical series no. 82.	Revision made.
Global Industry Coalition	121	42	**Replace** *"causing"* with *"having the potential to cause..."*	Editorial suggestions noted.

Global Industry Coalition	121	43	**Insert** at the end of the sentence additional text *", however in this example the measures were ultimately not successful.*"	Editorial suggestions noted and Revision made.
PRRI	121	25-26	These examples may also fall into biological or chemical weapons and be treated under the appropriate conventions and other instruments.	Editorial suggestions noted.
Western Michigan University	121	31-33	This sentence needs to be rewritten to be fully understandable.	Editorial suggestions noted. Revision made.
Global Industry Coalition	122	01	**Keep consistent,** *"Biotech"* is referred on previous page as "EC-Biotech" (no italics)	Editorial suggestions noted and revisions made.
Global Industry Coalition	122	36	**Revise for completeness.** The text stating "*outdoor ponds of algae … may be accessible to wildlife*". Such ponds would likely be contained in some way, e.g. they would be subject to specific risk management containment measures identified as part of a case-by-case risk assessment (e.g. suitable fencing to keep wildlife out).	Editorial suggestions noted.
Global Industry Coalition	122	32-34	**Delete** sentence "*At this point……often invoked*". This is inconsistent with other segments in the text. The inclusion of this statement raises the question why there is such a strong focus in the text to genome editing in agriculture? Please also note that the primary use of crops is for food and feed.	Editorial suggestion noted.
Global Industry Coalition	123	27	**Insert** *"defined as"* before *"living plants"*	Editorial suggestions noted and revisions made.
Global Industry Coalition	124	7	**Delete** *"for the case of living modified organisms"*	Editorial suggestions noted and revisions made.
Global Industry Coalition	124	9	**Delete** *"rather"*	Editorial suggestions noted and revisions made.

Global Industry Coalition	125	33	**Replace** "*apply"* with "*be relevant*"	Editorial suggestions noted and revisions made.
Western Michigan University	125	38	Delete the letter l.	Editorial suggestions noted and revisions made.
IWF	125	38	The letter I should be omitted.	Editorial suggestions noted and revisions made.
Global Industry Coalition	125	38	**Replace** "*apparent gaps and overlaps associated to the l*" with "*aspects of the*". It is inevitable that different synthetic biology uses and outcomes are regulated under different regulatory frameworks, that may or may not overlap, depending on the nature of the product and its intended use. Please make it clear in the text that there will be more than one regulatory regime that is applicable to any given product and/or use of synthetic biology. As it reads now, it appears that the authors are making an assumption that this should not be the case, i.e. that only a single regulatory regime is appropriate.	Editorial suggestion noted.
Global Industry Coalition	125	38	**Insert** "*and the ...*" after "*synthetic biology*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	125	01-02	**Delete**: "*and in terms of possibly producing adverse health effects*".	Editorial suggestion noted.
Global Industry Coalition	125	13-20	Please clarify text to reflect that these standards are generally the basis of food safety regulation, which includes foods derived from LMOs.	Editorial suggestions noted Revision made.
Global Industry Coalition	125	39-40	**Delete** "*associated to this scenario are also discussed*".	Editorial suggestions noted and Revision made.
Global Industry Coalition	126	02	**Insert** "*nor is it exceptional*" after "*duplication*".	Editorial suggestions noted and Revision made.

Global Industry Coalition	126	03	**Replace** "*discussed or considered under*" with "*within the scope of*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	126	04	**Insert** "*considered*" after "*but*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	126	07	**Delete** "*Although synthetic biology is often referred to as a single discipline, the*". This is not correct (see previous comments on the same statement).	Revision made.
Global Industry Coalition	126	08	**Insert** "*of synthetic biology, the unclear distinction between synthetic biology and "older" biotechnology that is the foundation of synthetic biology, and the numerous areas of research that are included as synthetic biology in this document...*" after "*definition*" and **delete** "*and the numerous areas of synthetic biology research*".	Editorial suggestions noted. Revision made.
Global Industry Coalition	126	14	**Insert** "*Rather, there is an*" after "*biology*" and **delete** "*The*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	126	14	**Insert** "*collection of*" after "*extensive*"	Editorial suggestions noted and revisions made.
Global Industry Coalition	126	14	**Insert** "*that potentially* " after "*mechanisms*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	126	16	**Delete** "*the rapid pace of*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	126	21	**Replace** "*fragmented"* with "complex".	Editorial suggestions noted. Revision made.
Global Industry Coalition	126	37	**Delete** "*upstream*" and "*market ready*"	Editorial suggestions noted and revisions made.
JCVI	126	11-15	I think it is important to point out that this is as it should be. Synthetic biology is too broad a collection of tools and can be applied to so many and	Editorial suggestions noted.

			varied applications that "no specific governance… on an international scale" would be possible or appropriate.	
Global Industry Coalition	126	19-20	**Delete** "*and therefore, they were not developed with the necessary scope and scale that some of the potential impacts of synthetic biology may present."* and **replace with** "*and while it is possible that they may not presently provide the necessary scope to address some of the potential impacts that synthetic biology may present in the future, such limitations were not clearly identified in this review*". The conclusion of the authors cannot be made on the basis of the term "synthetic biology" not being used, when they have basically used it themselves as a replacement term for "biotechnology", which is defined, and for which there are established regulatory mechanisms. The text needs to be factual and balanced.	Editorial suggestions noted. Revision made.
Global Industry Coalition	127	05	**Replace** "*offers*" with "*elaborates*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	127	10	**Replace** "*its Nagoya – Kuala Lumpur*" with "*the*" since this has been abbreviated to "*Supplementary Protocol*" previously.	Editorial suggestions noted and revisions made.
Global Industry Coalition	127	22	**Replace** "s*ynthetic biology, a closer examination concerning"* with *"biotechnology more generally, consideration of"*	Editorial suggestions noted. Revision made.
Global Industry Coalition	127	24	**Insert** "*may be relevant to consider, with the potential for greater collaboration in the future*." after "*Protocols*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	127	33	**Replace** "*were*" with "*maybe*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	127	04-07	**Revise** to clarify that the Cartagena Protocol is not limited to the risk of harm "caused by the transboundary movement of LMOs". It applies to the safe transfer, handling and **use** of LMOs, with specific focus on transboundary movements (Art 1). Generally, regulators will apply the same risk assessment	Comment noted

			processes irrespective of whether or not a transboundary movement precedes the **use**.	
JCVI	127	20, 21	This is not correct. Nefarious applications of synthetic biology have been discussed under the Biological Weapons Convention.	Editorial suggestions noted.
Global Industry Coalition	127	23-24	**Replace** "*appears likely and this will likely take into consideration of"* with "*will likely continued to be monitored and"*	Editorial suggestions noted.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	127	39-41	It should be clearly stated here that self-regulation cannot be the key to appropriate international regulation and governance of synthetic biology. This is the task of national and international regulatory bodies and not the synthetic biology community.	Editorial suggestions noted. Revision made.
IWF	128	08	WHO policies are described in their guidance document, do consider that in the report	Observations noted.
Global Industry Coalition	128	14	**Replace** "*can*" with "*could potentially*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	128	16	**Insert** "*public*" after "*biology*".	Comment noted.
Global Industry Coalition	128	17	**Insert** "*LM*" before "*mosquitoes*".	Editorial suggestions noted and revisions made.
JCVI	128	26	Following section "10.1 Risk of Harm," the report needs a section "10.2 Balancing Risks and Potential Benefits." In my opinion, this is the single greatest challenge associated with synthetic biology governance (the topic of Section 10). Though the report stresses the varied nature of the products using synthetic biology techniques, Section 10 overlooks this. How one balances risks and harms from simple crop genome editing (e.g., SDN-1) vs gene drives will be very different. Some of this is alluded to in lines 15 through 19 on this page. The WHO will view gene drives "through the lens"	Comment noted. Revision made.

			of 500,000 deaths/year from Malaria. FAO will view genome editing through the opportunities it provides for food security.	
Global Industry Coalition	128	28	Delete "*s*" from "*haves*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	128	34	**Insert** "*the strong participation of the conservation community, and* " after "*given*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	128	38	**Insert** "*Policy development by the IUCN is likely to influence synthetic biology discussions under the Convention and its Protocols*" after "*governance*".	Editorial suggestions noted and revisions made
Global Industry Coalition	128	43	**Insert** "*under these treaties*" after "*underway*".	Editorial suggestions noted and revisions made
Global Industry Coalition	128	44	**Insert** *"(if any)"* after "*obligations*".	Editorial suggestions noted and revisions made
Global Industry Coalition	128	45	**Insert** "*the tools and technologies used in* " after "*for*".	Editorial suggestions noted and revisions made
Global Industry Coalition	128	45	**Insert** "*the resulting*" after "*biology*".	Editorial suggestions noted and revisions made
Global Industry Coalition	128	45	**Replace** "*developed using*" with "*that use*".	Editorial suggestions noted and revisions made
JCVI	128	48	Subsection 10.3 omits the potential benefits from the tools of synthetic biology as enabling technologies that will allow countries to benefit from their own genetic resources. "Classical" 20th century tools of biotechnology were far less capable for harnessing genetic resources in productive ways. This is not just as issue of DSI.	Observation noted.
Global Industry Coalition	128	01-02	**Revise** for completeness. We question the conclusion of the authors about gaps due to the lack of a treaty regime. National governments are and will be able to determine if additional regulatory oversight is necessary.	Revision made.

Western Michigan University	128	08-09	However, the WHO would not allow or prohibit synthetic biology products per se; but rather would recommend whether a product could be used, based on its review that would include safety and efficacy considerations. Guidance documents issued by the WHO describe those considerations.	Comments noted.
Global Industry Coalition	128	09-10	**Delete** "*somehow implies that there could be potential interactions amongst various organisations in relation to*" and **replace with** "*suggests that it would be beneficial for the international organisations with overlapping mandates to collaborate in relation to ...".*	Editorial suggestions noted and revisions made.
Global Industry Coalition	129	03	**Insert** "*under UNCLOS*" after "*jurisdictions*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	129	04	**Delete** "*on this issue*.".	Editorial suggestions noted and revisions made.
Global Industry Coalition	129	10	**Delete** "*also*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	129	16	**Insert** "*specifically,* "after "*biology*"	Editorial suggestions noted and revisions made.
Global Industry Coalition	129	22	**Insert** "*those developed by*" after "*such as*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	129	23	**Delete** "*significant*".	Editorial suggestions noted and revisions made.
UN Div. Ocean Affs.	129	02-03	Change "an agreement for marine biodiversity beyond national jurisdictions" to "an international agreement on the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction"	Editorial suggestions noted and revisions made.
JCVI	129	25, 26	Again, "synthetic biology" covers too many technologies to allow such general statements as "many potential synthetic biology organisms may not	Revision made.

			be easily detectable". This is true only when the changes to the genome are so minor as to not be differentiated from mutations that might occur naturally.	
Global Industry Coalition	129	29-47	Delete This section should be deleted because it is redundant with Section C. In the first paragraph, the comment on sequencing has already been made elsewhere in the text. The "knowledge gap" referred to in the second paragraph (lines 34-37) simply reflects that this is an evolving area of science, not a mature field. The comment about "delivering on its promise" (line 33) is pointless. If there is such view, it is the result of the sensational language used in connection to synthetic biology. The oft-repeated "rapid pace of development" is an example of this - there is no justification for this claim. This is, in our view, supported by the factual examples presented in the report which show that there is very little "synthetic biology". The computing information in the third paragraph (lines 38-47) should be moved into the "supporting technologies and tools" section (Section C starting on page 16).	Revision made.
JCVI	129	32-33	This is a very odd way to characterize an article that concludes "synthetic biology is at the cusp of many major breakthroughs." Glass half empty vs glass half full…	Revision made.
GJSG on SynBio	129	34-37	This knowledge gap affects all approaches of breeding and engineering organisms. However, the DBTL cycle of synthetic biology achieves the highest levels of understanding of a GMO and its properties, thus minimizing potential side-effects.	Revision made.
JCVI	129	34-37	Of course there is a "knowledge gap" in how nature works. The authors should explain that the T and L in DBTL stand for "test and learn" and the reason it is called a "cycle" is that process is iterative, with redesign based on the knowledge gained through each iteration. This is one of the most powerful aspects of synthetic biology. Narrowing the knowledge gap about how the organism works is very much part of the process.	Revision made.

Global Industry Coalition	130	02	**Replace** "*are as equally*" with "*may be as*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	130	02	**Insert** "*in some countries*" after "*important*".	Editorial suggestions noted.
Global Industry Coalition	130	04	**Insert** "*advanced stages of development or*" after "*that*".	Editorial suggestions noted.
Global Industry Coalition	130	05	**Revise** the comment "*relatively little real-world data*" – there is ample relevant real-world data for existing LMOs, including SEC benefits.	Comment noted. Revision made.
JCVI	130	06-08	I do wish that the authors would expand on the lessons learned from "previous experience with classical genetical engineering". Again, the most authoritative review I know of is "Genetically Engineered Crops: Experiences and Prospects", NASEM, 2016. This would be helpful for readers who have only heard the "hypothetical/speculative concerns.	Comment noted. Revision made.
Global Industry Coalition	130	08	**Replace** "*classical*" with "*applications of*" **Delete "and associated concerns"**	Editorial suggestions noted. Revision made.
PRRI	130	08-09	Social-economic considerations on decision making may be considered as appropriate, they may be relevant in some instances but not necessarily beneficial in all situations.	Comment noted.
Global Industry Coalition	130	09	**Delete** "*has been somewhat absent*" and **replace** with "*has not been visible*". Although benefits many not be assessed under the GM risk assessment in many countries it does not mean it is absent.	Editorial suggestions noted and revisions made.
Global Industry Coalition	130	09-10	**Delete** "*a situation exacerbated by the lack of agreed international standards with respect to the types of data to collect, and how, for each type of application.*"	Editorial suggestions noted.
Global Industry Coalition	130	13	**Delete** "*socio economic and political*".	Editorial suggestions noted.

Global Industry Coalition	130	13	**Delete** "*very*".	Editorial suggestions noted and revisions made.
JCVI	130	14-38	Again, such broad generalizations about synthetic biology are not warranted nor are they helpful. Do all applications of synthetic biology require "inclusive decision-making and community engagement"? I hope the authors do not mean to imply that most synthetic biology research is irresponsible, but that is the conclusion from such sweeping and misleading generalizations. Is FPIC appropriate for all applications? This section needs to be sharpened, with generalizations deleted.	Revision made
ETC Group	130	24	Indigenous Peoples and Local Communities IPLC) will require resources to conduct their own collective discussions and decision making as part of adequate FPIC (wrongly abbreviated to FFIC on line 23). Their should be an obligation to provide these resources.	Comment noted.
African Centre for Biodiversity	130	24	IPLCs require resources to be able to conduct their own risk assessment, as well as for collective discussions, and decision making as part of genuine FPIC (wrongly abbreviated to FFIC on line 23) There should be an obligation to provide these resources.	Comment noted.
Global Industry Coalition	130	41	**Replace** "*concerns*" with "*involves*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	130	42	Please clarify the term "*non-traditional*"?	Editorial suggestions noted and revisions made.
Global Industry Coalition	130	44	**Insert** "*the"* before "*research".*	Editorial suggestions noted and revisions made.
Global Industry Coalition	131	02	**Delete** "*real or apparent*".	Editorial suggestions noted.
Global Industry Coalition	131	03	This line mentions "*independent*". It should be noted that the developer being a source of information is not an issue if there is transparency. Some	Revision made.

			role for developers in providing information will be needed because they will have the most scientific expertise about the project and are generating information following regulatory requirements for data generation in support of their applications.	
PRRI	131	04-07	For the adequate participation of all sectors of the society in decision taking adequate understanding is needed not only by the IPLCs but by different sectors of the society.	Comment noted.
Global Industry Coalition	131	18	**Replace** "*And*" with "*Also".*	Editorial suggestions noted and revisions made.
Global Industry Coalition	131	21	**Delete** "*moving*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	131	21	**Delete** "*to*" from "*into*".	Editorial suggestions noted and revisions made.
Western Michigan University	131	23	The acronym should be FPIC.	The acronym is not used at this location. We assume you are referring to the typo on page 130 line 24 (which has now been rectified).
Global Industry Coalition	131	31	**Replace** "*of*" with "*and*"	Editorial suggestions noted and revisions made.
Global Industry Coalition	131	34	**Replace** "*predominantly with research, handling, release and standards*" with "*with containment measures and release procedures*."	Editorial suggestions noted.
Global Industry Coalition	131	37	**Delete** "*far*".	Editorial suggestions noted and revisions made.

Global Industry Coalition	131	07-12	There are more examples of community participation that could be mentioned here, and it could also be mentioned that community participation is not limited to developing countries or IPLCs. An often-cited example (amongst others) that provides a basis for LM mosquitoes containing engineered gene drives is that undertaken for releases of Wolbachia infected (non-LM) mosquitoes in northern Australia.	Comment noted.
UK EBLC	131	21-23	The proposed holistic approach that looks beyond the standard synthetic biology issues of biosafety, health and environment is much needed. Synthetic biology, along with other novel technologies will have global impact and with this will bring forth new dilemmas and concerns regarding social, economic and ethical issues, and therefore it merits the inclusion of wider communities and social sciences perspectives. We fully agree with the view that the integration of responsibility and consideration of ELSI alongside research and product development is the right way forward. In the UK, Responsible Research and Innovation was set as one the bulwarks of the UK Synthetic Biology Roadmap https://ktn-uk.org/perspectives/a-strategic-roadmap-for-synthetic-biology-in-the-uk-2012/ and we have built an explicit requirement to have satisfactorily considered how these matters of responsibility will be addressed directly into the mechanisms for research funding, in addition to supporting numerous workshops and outreach activities relating to advancing this agenda. We have also pioneered the development of Standards and Guidelines for Responsible Innovation, via the bsi: 'PAS 440:2020 Responsible Innovation – Guide' https://pages.bsigroup.com/l/35972/2020-03-17/2cgcnc1 which is being eagerly adopted by businesses (more than 1000 downloads already). Whilst such approaches are broadly applicable beyond the field of synthetic biology alone, it is evident that the synthetic biology community has consistently demonstrated willingness to develop best-in-field approaches to the holistic evaluation of future innovations. By comparison, due to the large number of synthetic biology initiatives (academia, private sphere, government, NGOs, etc) the consultations proposed in the document with wider publics do not seem practical or realistic. It is very unclear how they expect to organise and streamline those	Comment noted.

			consultations?, how long would they last? what happens if no consensus is met in regards of new synthetic biology research projects, applications or deployment? It just feels like a poorly defined "wish list" of engagement and consultative activities rather than a strong roadmap that could both harness the impact of synthetic biology and at the same time do so in an equitable, fair, sustainable and responsible way. Thus, we feel strongly and agree that 'Social, economic and cultural concerns should be evaluated alongside scientific predictions', but these should be done within a pragmatic and down to earth approach that recognises and embraces the speed at which the field is moving.	
JCVI	131	36-38	Another sweeping generalization that is misleading. As pointed out earlier in the document, most products will be adequately covered by existing governance frameworks. Others are being adapted in real time (e.g., genome editing), as pointed out in several reviews referenced in the report. Clearly some are posing challenges.	Comment noted. Revision made.
Global Industry Coalition	131	36-38	**Revise** for factualness. There is no evidence to support multiple elements of this sentence: "The rapid advancement of the underlying science … ….the exponential rise in potential applications … …far exceeding the speed at which national and international governance frameworks can adapt" This over-stated language is not balanced or factual.	Comment noted. Revision made.
Global Industry Coalition	131	40-44	Regarding the "*challenge will be in arriving at international consensus*". International consensus and international rules are not always necessary - international instruments provide an internationally agreed frameworks/guidelines/recommendations etc. but ultimately countries will determine what and how they want to regulate.	Comment noted.
EBRC	131	42-44	This would be a very unfortunate outlook/outcome in the context of pressing global challenges and potential of synthetic biology to address these in a	Comment noted.

			disruptive manner. CBD should enable critical, constructive debate leading to reasonable implementable practices at short notice.	
Global Industry Coalition	131	42-44	**Delete** "*As in the case of challenges arising from the differences between a product-based and a process-based approach to regulation for classical genetic engineering, it is to be expected that similar if not greater challenges will continue to be faced for those organisms resulting from synthetic biology*." and **replace** with "*It is expected that challenges arising from differences in regulatory approaches for biotechnology (e.g. process-based versus product-based) will continue to be faced for those organisms resulting from synthetic biology*."	Editorial suggestion noted and Revision made.
Global Industry Coalition	132	07	**Delete** "*commercial deployment and*"	Editorial suggestion noted. Revision made.
Outreach Network for Gene Drive Research	132	07-09	Gene drive research is mostly still at an early stage, so this technology may not represent the most "useful lens through which to evaluate overlaps and potential gaps in the governance of synthetic biology".	Comment noted. Revision made.
JCVI	132	07-30	I agree that gene drives "provide a useful lens" for considering the governance of at least a few of the proposed applications of synthetic biology. (I also agree with the conclusion stated in lines 27-30.) But when presented as the sole "lens", it is actually quite misleading. Another example (perhaps genome editing, products intended for contained use, or even both) would illustrate the difficulty and even danger from attempting to draw general conclusions about such a varied set of potential applications as is anticipated from synthetic biology.	Comment noted. Revision made.
Western Michigan University	132	08	Engineered gene drives provide a useful lens through which to evaluate overlaps and potential gaps only to the extent that the research and development of these organisms has progressed. Gene drives have not progressed very far down the development pathway.	Comment noted. Revision made.
Imperial College London	132	08	Again, engineered gene drives are not close to release.	Comment noted. Revision made.

Global Industry Coalition	132	13	**Insert** "*likely*" after "*will"*.	Editorial suggestions noted and revisions made.
Global Industry Coalition	132	13	**Insert** "*more than one*" before "*national*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	132	13	**Insert** "*who will need to work together*" after "*authorities*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	132	14	**Insert** "*consistent with international recommendations for the development of these LMOs (e.g. NASEM 2016, WHO guidance framework 2014, 2021).*" after "*stepwise approach*",	Editorial suggestion noted.
Global Industry Coalition	132	17	**Insert** "*efficacy with regard to its intended public health use*" after "*demonstrate*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	132	17-20	**Delete** "*a positive impact for disease control. Such diverging orientations could pose practical challenges in the design of field evaluations of engineered gene drive organisms, especially when aiming to minimise risk while demonstrating positive health impacts.*". This is creating/overstating a problem - these objectives are not mutually exclusive. Any field evaluation of an LMO is for a particular purpose, and it can be designed according to more than one regulatory requirement. Addressing different regulatory assessment end points is not that hard in practice.	Editorial suggestion noted. Revision made.
Global Industry Coalition	132	19-22	**Replace** the following sentences "*It shows that issues of interaction and coordination are potential shortcomings under a fragmented international regime. Such shortcomings have the potential to be further perpetuated and exacerbated by the absence of"* with: "*It shows that interaction and coordination amongst different regulatory agencies with overlapping responsibilities will be required.*"	Editorial suggestions noted and Revision made.

			Note: The use of "*fragmented*" in line 21 is misleading. It is not "fragmented", there are just multiple regimes to comply with depending on the application. This is not unusual. e.g. a GM crop field trial may require coordination between LMO regulators, pesticide regulators, and/or therapeutic goods regulators.	
Global Industry Coalition	132	22	**Insert** "*This situation could be assisted by*" prior to *"integrated guidance provided under each regime or implementation under national law.*"	Editorial suggestion noted.
Western Michigan University	132	23	See above comment to p. 96, line 4 for the references to these guidance documents.	Revision made.
Global Industry Coalition	132	25	Please **provide references** to the two WHO recommendation documents.	Revision made.
Global Industry Coalition	132	26	The discussions under the CBD and Protocols referred to will be duplicative and redundant unless there is coordination with the WHO on mosquitoes	Comment noted.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	132	27	It should state "living modified organisms containing engineered gene drives"	Editorial suggestions noted and revisions made.
Western Michigan University	132	31	However, measures to control disease vectors by means such as pesticides, and generally human intervention in nature, including the development of agriculture, are interventions in nature that cannot be avoided.	Comment noted.
Imperial College London	132	31-32	Current interventions e.g. use of insecticides are already intervening in nature but are needed for control of vector borne diseases.	Comment noted.
Imperial College London	132	31-35	How does this consideration compare to current interventions?	Comment noted. Revision made.
PRRI	132	44	It needs to clarify the time frame that fall into what is referred as nearing commercial release and which are the applications. Please include references.	Revision made. Clarification in this regard can be found in section 3.

Global Industry Coalition	132	44	**Delete** "*exponentially*" as there is no evidence for this in this document.	Editorial suggestions noted and revisions made.
Global Industry Coalition	132	44	**Insert** "*under research, in development, or*" after "*applications*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	132	45	**Delete** "*solve*" and replace with "*contribute to addressing*".	Editorial suggestions noted and revisions made.
Global Industry Coalition	132	49	**Replace** "*become available*" with "*are envisioned*".	Editorial suggestions noted and revisions made.
DER VBIO & GASB	132	48f	As the field continues to advance and more applications become available, there is a growing pressure towards achieving clarity. We fully agree that clarity about concept und definition of synthetic biology is a precondition for any regulation and notice the lack of clarity. We want to emphasize that, in our view, a clear, mutually agreed definition of what falls under the term "synthetic biology" is the precondition for any discussion on specific regulations. We hope that the upcoming discussion will focus on defining synthetic biology within the CBD and its Protocols in order to move the discussion forward.	Comment noted.
Global Industry Coalition	133	03	**Replace** "*shown significant growth*" with "*grown*".	Revision made.
Global Industry Coalition	133	03	**Delete** "*goes in line*" and replace with "*is consistent*".	Revision made.
IWF	133	03-04	Mention the source and references	Comment noted.
PRRI	133	05-12	Some of these examples are usually not considered synthetic biology. There was no reference in the text of commercialization of products, it is better to clarify which products were approved for commercial release and are actually commercialized/available in the market.	Comment noted.

Global Industry Coalition	133	07	The genome edited soybean product referred to is not an example of synthetic biology.	See scope and methods for more clarity on definition and scope.
Global Industry Coalition	133	08	The self-limiting insects referred to are not an example of synthetic biology. They are "classic" LMOs that are assessed under existing regulatory frameworks. The first generation of these were developed in 2002, with field trials conducted before the 2015 synthetic biology technical series.	Revision made.
Outreach Network for Gene Drive Research	133	08-10	As mentioned earlier reference to engineered gene drives here is inaccurate, as they are not considered to be "in the advanced stages of development".	Revision made.
Global Industry Coalition	133	09	**Delete** "*advanced stages of*". These are not advanced when still completely in small-scale contained experiments.	Revision made.
Global Industry Coalition	133	09	**Delete** "*genome edited animals and*" as these are not examples of synthetic biology.	Revision made.
Western Michigan University	133	09-10	Not in advanced development.	Revision made.
Imperial College London	133	09-10	Again, engineered gene drives are still in the research and development phase and not close to potential release	Revision made.
Global Industry Coalition	133	12	**Delete** "*and*" and replace with "*will progress to*".	Revision made
Global Industry Coalition	133	12	**Delete** "*and development*"	Revision made
Western Michigan University	133	14	Also add the Genetic Engineering and Society Center at North Carolina State University (https://research.ncsu.edu/ges)	Comment noted.
Global Industry Coalition	133	14	**Delete** "*Despite*" and replace with "*With*"	Editorial suggestion noted and Revision made.

Global Industry Coalition	133	14-20	**Delete this entire paragraph** For the first two sentences (lines 14-16) – Is this really necessary on a general scale? Possible impacts will be discussed on a case by case basis. For the last sentence (lines 16-20) – as we have already commented, the term synthetic biology means the same thing as pre-existing "biotechnology" language. The scope of synthetic biology presented in this paper is as broad as possible, and still there are no examples that are outside the scope of existing regulatory mechanisms.	Editorial suggestion noted.
JCVI	133	21-23	Rather than referring to the discussions in Section 5, I think it makes more sense to review the applications discussed in Section 3. Yes, some will "challenge regulatory oversight", most will not.	Comment noted. Revision made.
Global Industry Coalition	133	25	**Insert** "*legislation and"* after "*existing*".	Editorial suggestions noted and Revision made.
Global Industry Coalition	133	27	**Delete** "*some of*".	Editorial suggestions noted.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	133	28	It might better read "the current potential inability to"	Editorial suggestions noted. Revision made.
Global Industry Coalition	133	28-29	**Delete** "*the inability to potentially detect and identify the applications of synthetic biology*" and **replace with** "*challenges with detection and identification of certain organisms discussed in this document."*	Editorial suggestions noted.
PRRI	133	28-30	Detection for all products derived from synthetic biology may not be necessary or useful.	Comment noted and Revision made.
Global Industry Coalition	133	30	**Insert** "*However, implementation and capacity challenges are not unique to synthetic biology and are the subject of extensive discussion under the Convention and Cartagena Protocol.*" at the end of sentence after "*developed*".	Editorial suggestions noted and Revision made.

Global Industry Coalition	133	32	**Delete** "*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"** and **replace with** : "*international regimes as silos, perhaps taking an overly simplistic view that if a specific international regime does not exist then regulation must be absent. This is misleading. The example given above for LM mosquitoes containing engineered gene drives highlights the need for relevant international regimes to collaborate on issues of overlapping concern*."	Comment noted.
Global Industry Coalition	133	33	**Delete** "*to expand the focus of the governance*" and **replace with** "*We also assert that the focus of governance should be expanded ....*" It needs to be made clearer that this is the view of the authors.	Comment noted.
Global Industry Coalition	133	35-47	The content in this paragraph following "*Responsible research and innovation*" is all new information, it belongs in the main body of the document, not the "conclusions".	Comment noted. Revision made.
Global Industry Coalition	134	02	**Provide a weblink** in footnote for COP decision 14/19	Editorial suggestions noted and Revision made.
Western Michigan University	134	03-04	References to this work should be provided.	Revision made.
Outreach Network for Gene Drive Research	134	03-04	Citations for the "scientific research addressing community engagement in field trials, concerning for instance engineered gene drive organisms (i.e. for malaria control)" should be included.	Revision made.
Global Industry Coalition	134	03-12	This paragraph is new information, relevant to section 10.6 -it should go there, not in the "conclusion". Lines 3-4 need to include references to the cited work.	Revision made.
ETC Group	134	20	Insert the sentence: "FPIC should follow principles that are proposed by IPLCs themselves, which will differ depending on their cultural, geographical and political contexts".	Comment noted and revision made

African Centre for Biodiversity	134	20	Insert the sentence: “FPIC should follow principles that are proposed by IPLCs themselves, which will differ depending on their cultural, geographical and political contexts”.	Revision made.
Global Industry Coalition	134	21	**Replace** “*form*” with “*from*”	Editorial suggestions noted and revisions made.
Western Michigan University	134	22	change “form” to “from”	Revision made.
GJSG on SynBio	134	29-32	Engineered organisms produced by synthetic biology methods represent no further risks when introduced into the environment than a given non-GMO or GMO organism. Therefore, it is not appliable to evaluate them on different grounds. Gene drives require regulatory oversight.	Comment noted.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	134	29-33	It has to be taken into account here that possible environmental risks are not side effects that could occur in parallel to a potential beneficial solution. Applications aiming at “unprecedented environmental challenges“ can only have benefits if adverse effects on the environment can be ruled out in advance. For most applications data on actual benefits and their actual (positive or negative) impact on environment is still incomplete. Please consider to exchange “Despite its potential benefits“ for „However actual benefits are yet mostly unclear and”. In order to clearly catch its intention line 31 should also read: “significant negative impacts”	Revision made.
Global Industry Coalition	134	29-43	The conclusion section is too long - too repetitive, and too much new information is introduced. It should be a clearly written summary. Specifically, the paragraphs running from lines 29-38 and 39-43 are repetitive and unnecessary. In addition, in line 43, there is a suggestion that certain international laws are ill-equipped? What specifically makes them “ill-equipped”? this is not demonstrated in this document which merely reviews (does not assess or evaluate) legal provisions.	Revision made.

Imperial College London	134	31-32	Which is case specific and cannot be generalised	Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	134	44	"The overlaps and gaps identified in this update suggest that opportunities exist for increased coordination amongst the Convention and its Protocols, and with other relevant international treaties, processes and initiatives converging on the governance of synthetic biology." It should be noted that different conventions, treaties, processes and initiatives have diverging goals, which questions whether "increased coordination" is appropriate here. The CBD recognizes such differences by the category of "biodiversity-related conventions" (see e.g. CBD COP Decision 14/30) The second part of the sentence could be rephrased by including "for increased information exchange" before "with other relevant".	Editorial suggestions noted and revisions made.
Global Industry Coalition	135	13	**Delete** "*solving*" and replace with "*providing new tools and approaches for addressing"*.	Editorial suggestions noted and revisions made.
Global Industry Coalition	135	08-11	**Delete** these two sentences. What "gaps" are referred to here? The only "gap" might be national implementation, which is not specific to synthetic biology.	Revision made.
Member of AHTEG Synthetic Biology, Federal Agency for Nature Protection	135	13-14	It is not the task of the CBD and its organs to promote "research and development" in general. Nonetheless, I agree that it is imperative to prepare for appropriate regulation and risk assessment of Synthetic Biology in general. I propose to delete: "for research and development, and"	Revision made.