Global Industry Coalition
Submission of Information on Synthetic Biology

Ref: SCBD/CP/DC/MA/MW/87791 of 14-December-2018

15 February 2019

The Global Industry Coalition (GIC)[1] is pleased to make the following submission of information on synthetic biology in response to the request of the Executive Secretary[2] for "information and supporting documentation" on four topics from decision XIV/19 of the Conference of the Parties to the Convention on Biological Diversity (CBD). In this submission, the GIC provides an in-depth analysis of the four topics (A - D) listed in the decision and notification SCBD/CP/DC/MA/MW/87791. This submission is supported by recent peer-reviewed publications and information from relevant sources as noted.

A. The relationship between synthetic biology and the criteria set out in decision IX/29, paragraph 12, in order to contribute to the completion of the assessment requested in decision XII/24, paragraph 2, building on the preliminary analysis prepared by the Executive Secretary in document SBSTTA/22/INF/17;

SUMMARY: The question of whether synthetic biology is a new and emerging issue (NEI) relating to conservation and sustainable use of biodiversity remains unanswered despite extensive programs of work undertaken since 2010[3] by the CBD (technical reports, submissions of information and peer reviews, on-line fora, two Ad Hoc Technical Expert Group meetings and peer reviewed reports, and meetings of the Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) and Conference of the Parties (COP)). The GIC is of the view that the completion of a robust, factual, evidence-based,

[1] The Global Industry Coalition (GIC) for the Cartagena Protocol on Biosafety receives input and direction from trade associations representing thousands of companies from all over the world. Participants include associations representing and companies engaged in a variety of industrial sectors such as plant science, seeds, agricultural biotechnology, food production, animal agriculture, human and animal health care, and the environment.

[2] Notification Ref: SCBD/CP/DC/MA/MW/87791 of 14 December 2018.

[3] UNEP/CBD/COP/DEC/X/13.

and transparent NEI analysis that results in the identification of synthetic biology as a NEI should be a prerequisite for any on-going work on the topic under the CBD and its Protocols[4]. Our consideration of the criteria for identifying a NEI demonstrates that it cannot be concluded that synthetic biology qualifies. It is critical to recall items "(b) New evidence of unexpected and significant impacts on biodiversity" and "(c) Urgency of addressing the issue/imminence of the risk caused by the issue to the effective implementation of the Convention as well as the magnitude of actual and potential impact on biodiversity" of paragraph 12 of the Decision IX/29 as key indicators to be achieved aimed at considering an issue as a NEI. Further, despite extensive work conducted under the CBD over almost ten years, there is no evidence for specific regulatory gaps or biosafety risks associated with current or foreseeable applications that cannot be managed by existing regulatory approaches.

Decision IX/29

This topic refers to the necessary assessment for identifying a new and emerging issue relating to the conservation and sustainable use of biological diversity. The process is set out in Decision IX/29,[5] whereby proposals from "Parties and relevant organizations" are reviewed by SBSTTA, and in cases where SBSTTA identifies a NEI, it will "elaborate a scientific and technical analysis with options for action for consideration" by the COP. The GIC supports this process and its inclusion in the terms of reference for the AHTEG. As such, we strongly support the "…completion of a *robust analysis* using the criteria set out in paragraph 12 of decision IX/29" (emphasis added) as stated in the paragraph referred to in decision XII/24[6]. The GIC has long been of the view that the mandate of the AHTEG should be limited to addressing this analysis as a necessary first step to justify the commitment of extensive resources from both the Secretariat and Parties to work programs. In the absence of a determination by the Parties that synthetic biology meets the criteria for a NEI, the GIC questions the rationale for continued extension and expansion of the synthetic biology work program beyond information sharing as a means of horizon scanning through the Open-ended Online Forum.

For the topic of synthetic biology, NEI proposals were first made in 2010, and following consideration of submitted information that was invited[7] to address the decision IX/29 criteria, SBSTTA-18

[4] Cartagena Protocol on Biosafety to the Convention on Biological Diversity ("Cartagena Protocol"); Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation to the Convention on Biological Diversity ("Nagoya Protocol").
[5] UNEP/CBD/COP/DEC/IX/29.
[6] UNEP/CBD/COP/DEC/XII/24 paragraph 2.
[7] UNEP/CBD/COP/DEC/X/13.

concluded that there was "insufficient information to finalize an analysis of whether synthetic biology is a new and emerging issue"[8]. An extensive synthetic biology work program was subsequently established in 2014[9], extended in 2016[10] and again in 2018[11]. The synthetic biology work programs have included further submissions of information on a range of topics, some linked to the NEI criteria, as well as online discussions of these topics and deliberations by two AHTEGs (in 2015 and 2017). However, instead of these activities contributing to formally completing the requested NEI assessment, it has been left open for almost ten years, compromising the credibility of the whole NEI process and requiring substantial resource investment by all involved. During this time, "synthetic biology" has become the CBD mechanism for debating a vast array of early research concepts and enabling technologies that have emerged or been contemplated in the field of biotechnology, despite the fact that some of these technologies are not considered to be synthetic biology. The GIC stresses that technological developments are the logical consequence of accumulated knowledge and experience and are aimed at improved process efficiency and predictability of outcomes without necessarily creating new "issues".

The GIC notes that the terms of reference for the 2017 AHTEG included providing a recommendation to facilitate "an analysis against the criteria set out in paragraph 12 of decision IX/29 to contribute to the completion of the assessment requested in paragraph 2 of decision XII/24" by SBSTTA[12], but this was not undertaken and completed[13]. Instead the AHTEG deferred the analysis requested "… until further guidance was provided" from SBSTTA on how to apply the criteria of paragraph 12 in decision IX/29. This was on the agenda for SBSTTA-21[14], but no clarification on the application of the decision IX/29 criteria was elaborated in the decision[15]. The Secretariat then prepared a "preliminary analysis", "by linking relevant statements in the AHTEG reports to the criteria" of paragraph 12[16]. The GIC stresses that this does not in any way constitute a "robust analysis", and it does not comply with the mandate approved. As such, we are not in a position to support its consideration or use as a basis for the NEI analysis. The preliminary analysis by the Secretariat is problematic for at least two

[8] SBSTTA-18 Recommendation XVIII/7.
[9] UNEP/CBD/COP/DEC/XII/24.
[10] CBD/COP/DEC/XIII/17.
[11] UNEP/CBD/COP/DEC/XIV/19.
[12] UNEP/CBD/SYNBIO/AHTEG/2017/1/1; UNEP/CBD/SYNBIO/AHTEG/2017/1/3.
[13] CBD/COP/DEC/XIII/17.
[14] CBD/SBSTTA/21/1.
[15] CBD/SBSTTA/REC/XXI/7.
[16] CBD/SBSTTA/22/INF/17.

significant reasons. Firstly, because it is not clear how the Secretariat determined what constituted "relevant statements" for inclusion. Secondly, because AHTEG reports are not consensus documents; rather, they include the spectrum of views in the group, some of which may be held by one individual. The GIC stresses that these are methodological weaknesses that should invalidate the "preliminary analysis". In the absence of clear and transparent methodology and credible information, the document is indefensible and cannot contribute towards the robust assessment expected by Parties.

Paragraphs 11 and 12 of Decision IX/29

The criteria delineated in paragraph 12 of decision IX/29 are reproduced with our comments added below. As elaborated in the 2017 GIC submission on the NEI process[17] - a view supported by numerous Parties in their submissions and at the COP14 discussions - the GIC's view is that all of these criteria must be considered as a whole. In the present submission, the GIC has endeavored to provide a detailed consideration of synthetic biology in the context of each criterion. We also emphasize that the criteria of paragraph 12 should be viewed as building on the requirements of paragraph 11, also reproduced below, which provides the framework for a proposal. We note that it is challenging, if not impossible, to apply these criteria in a meaningful way to an undefined term like "synthetic biology", and we have focused on certain *applications* that have featured in the CBD synthetic biology discussions. **The GIC believes that for an issue to be considered against the criteria in decision XII/29, and to potentially meet those criteria, it must be a well-defined application that is intended to be released into the environment, e.g. a specific product**.

Paragraph 11 *"Decides* that proposals for emerging issues should, where possible, be accompanied with information on:

(a) Why the issue needs urgent attention by the Subsidiary Body on Scientific, Technical and Technological Advice (including how it impacts biodiversity);

(b) How it affects the attainment of the objectives of the Convention (citing relevant articles);

(c) Thematic programmes of work and/or cross-cutting issues that could contribute to the resolution of the issue;

(d) Work already under way by relevant organizations addressing the issue; and

[17] See: https://www.cbd.int/doc/emerging-issues/Global-Industry-Coalition-submission-2017-054-en.pdf.

(e) Credible sources of information, preferably from peer-reviewed articles;"

Paragraph 12 *"Further decides* that the following criteria should be used for identifying new and emerging issues related to the conservation and sustainable use of biodiversity:

"(a) Relevance of the issue to the implementation of the objectives of the Convention and its existing programmes of work;"

The relevance of the issue to the CBD should be clearly established as a first step. Our view is that synthetic biology falls within the definition of "biotechnology" under the CBD and "modern biotechnology" under the Cartagena Protocol and is therefore broadly relevant. However, an undefined field or group of "new" technologies as a whole cannot be considered against this criterion (or the other criteria of paragraph 12) in a meaningful way. We emphasize that relevance to the implementation of the objectives of the Convention can only be considered in the context of specific applications that are realistically foreseeable. This requires that they are plausible, technically feasible, and likely to be released into the environment in the foreseeable future – as opposed to speculation on the potential outcomes of every early research concept and enabling technology that emerges in the field. In our view, no *credible* information or evidence (using the language of paragraph 11(e)) has been presented demonstrating an *actual* or *potential* (using the language of other paragraph 12 criteria below) challenge to the implementation of the objectives of the CBD and its existing programs of work by any specific use of a product of biotechnology enabled by advances in synthetic biology. As we have noted above, establishing relevance according to this criterion, while important, is not a deciding criterion on its own and the other criteria of paragraph 12 need to be considered as a whole to identify a NEI.

The GIC emphasizes that the array of existing regulatory mechanisms that apply to biotechnology/modern biotechnology continue to apply to "synthetic biology" related activities and products. We have reviewed some of these in detail in our 2017 submission of information[18].

"(b) New evidence of unexpected and significant impacts on biodiversity;"

The GIC is not aware of, and does not believe that, any *credible* "new evidence of unexpected and significant impacts on biodiversity" has been provided in the CBD synthetic biology discussions. The

[18] Available at: https://bch.cbd.int/database/record.shtml?documentid=112053.

word “credible” is an important inclusion in paragraph 11(e) and it is necessary to provide balance against subjective opinions as being considered “evidence”. In the past, lists of examples have been provided of “new developments” often hypothetical, along with speculation of risk and outcomes that “might” occur[19] that are unsupported by credible evidence.

What constitutes an “impact” or an “unexpected” or “significant” impact is not defined, however guidance in the context of living modified organisms may be found in the Supplementary Protocol on Liability and Redress[20]. Also, considering the language of the other criteria of paragraph 12, which refer to “urgency” and “imminence of risk”, it is assumed that the “impact” needs to be negative or adverse. The Supplementary Protocol is concerned with “damage” that is “significant”, with “damage” defined as an “**adverse effect** on the conservation and sustainable use of biological diversity, taking also into account risks to human health, that is **measurable or otherwise observable taking into account, wherever available, scientifically-established baselines** recognized by a competent authority that **takes into account any other human induced variation and natural variation**…”[21] (emphasis added). Whether the damage/adverse effect is “significant” needs to be determined on the basis of factors such as[22]:

a. The long-term or permanent change, to be understood as change that will not be redressed through natural recovery within a reasonable period of time;
b. The extent of the qualitative or quantitative changes that adversely affect the components of biological diversity;
c. The reduction of the ability of components of biological diversity to provide goods and services;
d. The extent of any adverse effects on human health in the context of the Protocol.

We note that the concerns raised today about the potential impacts of “synthetic biology” echo those that were initially raised for biotechnology, and for its application to develop biotech crops in particular. Decades later there remains no credible evidence for “unexpected and significant impacts

[19] E.g. see: 2017 AHTEG report: UNEP/CBD/SYNBIO/AHTEG/2017/1/3 (page 3).
[20] Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol (Supplementary Protocol).
[21] Supplementary Protocol Article 2.2.
[22] Supplementary Protocol Article 2.3.

on biodiversity" of engineered organisms that have been released into the environment, or of "damage" in accordance with the Supplementary Protocol; in fact the opposite has been demonstrated with a large body of published evidence showing a range of beneficial outcomes[23]. Proper consideration of the elements of paragraph 11 would take into account and extrapolate from this corpus (i.e. credible information); however, it is largely overlooked in the CBD synthetic biology discourse.

"(c) Urgency of addressing the issue/imminence of the risk caused by the issue to the effective implementation of the Convention as well as the magnitude of actual and potential impact on biodiversity;"

The GIC emphasizes that the array of existing regulatory mechanisms that apply to biotechnology/modern biotechnology continue to apply to any risks presented by "synthetic biology" related activities and products. We also highlight there can be no "urgency" to address synthetic biology as an "issue" or "imminence of risk" caused by it. Firstly, an ill-defined field or group of technologies do not in themselves present regulatory challenges – regulatory clarity is often obtained upon introduction of a tangible, specific use. Secondly, as we have stated above for criterion (b), no *credible* evidence has been presented of unexpected and adverse impacts (actual or potential) on biodiversity. In the absence of regulatory gaps and any credible evidence of "actual" impacts there can be no "urgency" or "imminence of risk". Certain prominent elements of the CBD synthetic biology discourse are focused on "potential" impacts and their potential magnitude, which have been speculation driven and not based on credible evidence. Claims of urgency are most pronounced in regard to gene drives, and these are discussed in further detail under the paragraph 12 criteria that follow (criteria (d), (e) and (f), as well as topics B and C).

The GIC notes that unsubstantiated claims have been made that existing regulatory frameworks may not be adequate to handle the potential risks of synthetic biology. However, there have not been any identified cases of such challenges to risk assessment. In the risk assessment work program under the Cartagena Protocol, experienced biotech regulators could

[23] CropLife International has compiled an extensive, publicly-available, up-to-date database containing published literature that demonstrates benefits of biotechnology for the environment and for agriculture available at: http://biotechbenefits.croplife.org/.

not identify specific examples of current or foreseeable synthetic biology applications that presented novel regulatory challenges or biosafety risks that could not be managed using established regulatory approaches[24]. Further, a recent expert report (German Central Committee on Biological Safety, ZKBS[25]) specifically investigated the potential regulatory challenges arising from synthetic biology applications, and concluded that "the research approaches currently pursued in Synthetic Biology in Germany as well as worldwide involve **no specific risks for biological safety other than those already being assessed for "conventional" genetic engineering** by applying the GenTG [domestic regulatory framework] and other international regulations" (emphasis added)[26]. The GIC agrees with **many regulatory authorities who have stated that governance and adequate oversight are in place to allow continuous developments in the field of biotechnology, including also for current and foreseeable developments in synthetic biology.**

"(d) Actual geographic coverage and potential spread, including rate of spread, of the identified issue relating to the conservation and sustainable use of biodiversity;"

As alluded to earlier, assessing phenomena such as "actual geographic coverage and potential spread" requires having a tangible or defined product/organism as the subject of the assessment, as opposed to examples of enabling technologies. As we note for paragraph 12 criterion (c) above, discussions on "hypothetical" or "potential" rather than "actual" cannot lead to meaningful conclusions. We continue to assert that credible evidence only exists for specific products, for example biotech crops that have been released into the environment for more than twenty years. Further, concerns regarding their impacts on biodiversity, which include the impacts of gene flow such as transgene spread to wild relatives and invasiveness in natural habitats, have not eventuated despite releases into the environment of a scale

[24] E.g., see the online forum discussions: "*Submission of views, relevant guidance and sources of information on risk assessment of organisms developed through synthetic biology*" (9-23 May); and "*Possible considerations during the environmental risk assessment of LMOs developed or created through approaches commonly referred to as "synthetic biology"* (13-27 June) at http://bch.cbd.int/onlineconferences/2014_2016period.shtml.

[25] ZKBS advises the Federal Government and the Federal States in safety-relevant questions on genetic engineering.

[26] German Central Committee on Biological Safety (ZKBS) (2018). 2nd Interim report of the German Central Committee on Biological Safety, available at: https://www.zkbs-online.de/ZKBS/SharedDocs/Downloads/02_Allgemeine_Stellungnahmen_englisch/01_general_subjects/2nd%20report%20Synthetic%20Biology%20(2018).html?nn=8569050.

(commercial releases) of an accumulated 2.3 billion hectares over the 22 years since biotech crops were first commercialized[27]. These concerns were largely based on suggestions that the traits expressed by biotech crops would confer selective advantages outside of highly managed agricultural environments. The evidence supports ~800 regulatory approvals that have been granted between 1992-2017 in 40 countries[28] which conclude that biotech crops do not present any greater risk than their conventional counterparts. Conversely, there is a significant body of evidence demonstrating a range of environmental benefits[29].

Gene drives have become a predominant topic in the CBD synthetic biology discussions, with calls for a moratorium because of concerns regarding their potential geographical spread and hypothesized unintended and/or irreversible consequences. Organisms containing engineered gene drives are LMOs (per the Cartagena Protocol), but they differ from LMOs released into the environment previously in that they are designed, in theory, to spread in order to achieve the intended outcome, e.g. control of a vector-borne disease. The CBD discussions on gene drives overlook the current technical capabilities and status of gene drive research and instead create a false impression of technological probability and imminence of environmental release. It also overlooks the awareness of the gene drive research community of these concerns, and the cautious, step-wise and transparent approach it is taking to understanding the potential impacts of the technology[30].

The term "gene drive" refers to a range of genetic mechanisms that lead to the transmission of a specific allele (gene variant) with a frequency of greater than 50% to the next generation. In *theory*, a successfully engineered gene drive could lead to the preferential increase in the frequency of a specific genotype over many generations, and an entire population could eventually have that genotype[31]. As a first step, for an engineered gene drive to work, the

[27] International Service for the Acquisition of Agri-biotech Applications (2018) Global status of commercialised biotech/GM crops in 2017: Biotech crop adoption surges as economic benefits accumulate in 22 years. ISAAA Brief 53-2017.
[28] Ibid.
[29] See publications compiled in the CropLife International Benefits Database: http://biotechbenefits.croplife.org/.
[30] See e.g. Royal Society (2018) Statement: Gene drive research: why it matters.
[31] Australian Academy of Science (2017) Discussion Paper: Synthetic gene drives in Australia – Implications of emerging technologies.

target organism must have certain characteristics: sexual reproduction, short generation time (i.e. reproduces rapidly so that the gene can spread), and amenability to transformation (i.e. it is possible to insert a gene drive, creating a transgenic organism). Gene drives therefore would not be of practical relevance in viruses, bacteria, many plants and some animals, including humans[32]. The most technically advanced applications with real-world applications are currently in vector control and conservation[33]. Mosquitoes are the best example of the few cases where it is hoped that engineered gene drives will work[34], but they are not expected to be ready for field testing for at least five years[35].

Reports of proofs of concept or new developments in a laboratory with uniform populations and highly controlled conditions do not equate to imminent environmental release or fully operational technology in wild populations. The gene drive research community has identified significant technical challenges that must be overcome for engineered gene drives to work in wild populations, including fitness costs in organisms carrying the drive, and high rates of resistance evolution that inactivates the drive[36]. In a recent small-scale laboratory proof-of-concept study with caged mosquitoes (*Anopheles gambiae*), an engineered gene drive reached 100% prevalence within 7-11 generations[37]. The authors highlighted that these laboratory results do not rule out impacts on the fitness of organisms carrying the gene drive or that the gene drive won't be compromised by the development of resistance, and that further testing is required on a larger scale (in confined conditions) that more closely resembles native

[32] Ibid.
[33] Van der Vlugt CJB, Brown DD, Lehmann K, Leunda A, Willemarck N (2018) A framework for the risk assessment and management of gene drive technology in contained use. *Applied Biosafety* 23: 25-31.
[34] Australian Academy of Science (2017) Discussion Paper: Synthetic gene drives in Australia – Implications of emerging technologies.
[35] Target Malaria (2016) Open Letter on Gene Drive Technology. Available at: https://targetmalaria.org/open-letter/.
[36] Champer J, Liu J, Oh SY, Reeves R, Luthra A, Oakes N, Clark AG, Messer PW (2018) Reducing resistance allele formation in CRISPR gene drive. *Proceedings of the National Academy of Sciences USA* 115: 5522-5527; Callaway E (2017) Gene drives meet the resistance. *Nature* 542: 15; Drury DW, Dapper AL, Siniard DJ, Zentner GE, Wade MJ (2017) CRISPR/Cas9 gene drives in genetically variable and nonrandomly mating wild populations. *Science Advances* 3: e1601910 DOI: 10.1126/sciadv.1601910; Noble C, Olejarz J, Esvelt KM, Church GM, Nowak MA (2017) Evolutionary dynamics of CRISPR gene drives. *Science Advances* 3: e1601964; Unckless RL, Clark AG, Messer PW (2017) Evolution of resistance against CRISPR/Cas9 gene drive. *Genetics* 205: 827-841.
[37] Kyrou K, Hammond AM, Galizi R, Kranjc N, Burt A, Beaghton AK, Nolan T, Crisanti A (2018) A CRISPR-Cas9 gene drive targeting *doublesex* causes complete population suppression in caged *Anopheles gambiae* mosquitoes. *Nature Biotechnology* 36: 1062-1066.

ecological conditions[38]. In parallel to the much-hyped technological developments and laboratory-based research, the gene drive community is actively investigating the potential behavior of gene drives in wild populations based on modelling[39] before field releases are proposed. Another area of active investigation is mitigation, which is discussed in further detail under the following criterion (criterion (e)).

"(e) Evidence of the absence or limited availability of tools to limit or mitigate the negative impacts of the identified issue on the conservation and sustainable use of biodiversity;"

This criterion calls for evidence that risk management would be impracticable or unacceptably challenging. Regulators experienced with actual synthetic biology applications have already noted that this is not the case and this is not foreseeable[40]. In addition, the GIC notes that a previous CBD online discussion[41] and the 2017 AHTEG considered the related topic of "tools to detect and monitor the organisms, components and products of synthetic biology"[42]. The GIC agrees with the conclusion in the AHTEG report that tools in use for the detection, identification and monitoring of LMOs can be used for organisms developed through "synthetic biology" – or more precisely, that the tools exist to enable the development of specific methods for newly created LMOs i.e., products of synthetic biology.

As noted above, organisms containing engineered gene drives differ from LMOs released into the environment previously in that they are designed (in theory) to spread and persist. The scientific community has recommended the use of multiple confinement and containment strategies to reduce the potential for unintended releases during gene drive research and development[43]. Their research

[38] Ibid.
[39] See e.g. de Jong TJ (2017) Gene drives do not always increase in frequency: from genetic models to risk assessment. *Journal of Consumer Protection and Food Safety* 12: 299-307.
[40] E.g. see the online forum discussions: "*Submission of views, relevant guidance and sources of information on risk assessment of organisms developed through synthetic biology*" (9-23 May); and "*Possible considerations during the environmental risk assessment of LMOs developed or created through approaches commonly referred to as "synthetic biology"* (13-27 June) at http://bch.cbd.int/onlineconferences/2014_2016period.shtml.
[41] See: https://bch.cbd.int/synbio/open-ended/discussion_2017-2018/#topic3.
[42] 2017 AHTEG report: UNEP/CBD/SYNBIO/AHTEG/2017/1/3 (page 5).
[43] Akbari OS, Bellen HJ, Bier E, Bullock SL, Burt A, Church GM, Cook KR, Duchek P, Edwards OR, Esvelt KM, Gantz VM, Golic KG, Gratz SJ, Harrison MM, Hayes KR, James AA, Kaufman TC, Knoblich J, Malik HS, Matthews KA,

also includes investigation of mitigation strategies in the event of unintended release or consequences, and mechanisms that have been proposed include: molecular (e.g. separation of drive components) and physical confinement; geographical (e.g. trials in regions where there are no native populations of the target organisms), ecological or reproductive containment; the tandem use of immunization drives; the release of reversal drives to remove the initially introduced trait; and the use of drives designed to have limited spread (e.g. threshold dependent drives)[44]. It is also proposed that the presence and prevalence of drives could be monitored by targeted amplification or meta-genomic sequencing of environmental samples[45]. It is noteworthy that several mitigation strategies and combinations of these were also proposed for biotech crops in the early years of biotech crop commercialization in response to similar concerns[46].

We note above under paragraph 12 criterion (e) that the gene drive community is taking a cautious, step-wise and open approach in their research towards developing the technology and understanding its potential impacts. Their activities are in line with the COP14 decision on synthetic biology[47] that calls for a precautionary approach. The decision also calls for releases of organisms containing engineered gene drives to be considered on the basis of scientifically sound case-by-case risk assessments, with appropriate risk management measures in place to avoid or minimize potential adverse effects. The continuation of research is vital for informing and enabling risk assessment and for identifying appropriate risk management measures.

O'Conner-Giles KM, Parks AL, Perrimon N, Port F, Russell S, Ueda R, Wildonger J (2015) Safeguarding gene drive experiments in the laboratory – Multiple stringent confinement strategies should be used whenever possible, *Science* 349: 927-929; National Academies of Sciences Engineering and Medicine (2016) Gene Drives on the horizon: Advancing science, navigating uncertainty, and aligning research with public values. Washington, DC: The National Academies Press. DOI: 10.17226/23405.

[44] Australian Academy of Science (2017) Discussion Paper: Synthetic gene drives in Australia – Implications of emerging technologies; Royal Society (2018) Statement: Gene drive research: why it matters. See also Akbari OS, Bellen HJ, Bier E, Bullock SL, Burt A, Church GM, Cook KR, Duchek P, Edwards OR, Esvelt KM, Gantz VM, Golic KG, Gratz SJ, Harrison MM, Hayes KR, James AA, Kaufman TC, Knoblich J, Malik HS, Matthews KA, O'Conner-Giles KM, Parks AL, Perrimon N, Port F, Russell S, Ueda R, Wildonger J (2015) Safeguarding gene drive experiments in the laboratory – Multiple stringent confinement strategies should be used whenever possible, *Science* 349: 927-929.

[45] Oye KA, Esvelt K, Appleton E, Catteruccia F, Church G, Kuiken T, Lightfoot SB-Y, McNamara J, Smidler A, Collins JP (2014) Regulating gene drives. *Science* DOI: 10.1126/science.1254287.

[46] See e.g. Daniell H (2002) Molecular containment strategies for gene containment in transgenic crops. *Nature Biotechnology* 20:581-586.

[47] CBD/COP/DEC/14/19.

Another related issue discussed under this topic is whether organisms which contain mutations generated with the aid of genome editing tools should be considered as products of synthetic biology, and if they are, it might be challenging to use DNA detection methods for their detection and identification. The GIC has maintained that **genome editing is not synthetic biology**, rather it is a broad category of enabling tools that can be applied to achieve various outcomes (discussed in more detail below under topic B). In applications of genome editing that result in an organism considered to be an LMO, adequate detection tools can be developed as required using existing approaches.

"(f) Magnitude of actual and potential impact of the identified issue on human well-being;"

Many of the "new developments" in synthetic biology/biotechnology are aimed at human health applications, and these are often an indicator of how technology may develop in other sectors – the recombinant DNA technology giving rise to biotech crops, and more recently, genome editing in crops, provide examples of this. We have addressed the *actual* benefits of biotechnology in agriculture for human well-being, in terms of economic benefits, elsewhere in this submission (see especially paragraph 12 criterion (g) below, and topic C). It is anticipated that with technological development the range of benefits already demonstrated will continue to be provided. Furthermore, current research and development is aimed at improving upon these and providing an expanded range of benefits including improved nutrition, e.g. biofortified crops to address micronutrient deficiencies[48].

The potential impact of gene drives on human well-being provides a strong case against a moratorium. Gene drive research is most advanced for the application of controlling devastating human diseases spread by mosquitoes (e.g. Malaria, West Nile fever, Dengue fever, yellow fever, trypanosomiasis, Chikungunya, and Zika). Campaigns for a moratorium are based upon speculation about what gene drives *could* be used for without considering the human cost of not using them for their intended purpose. Malaria is a global public health

[48] Garg M, Sharma N, Sharma S, Kapoor P, Kumar A, Chunduri V, Arora P (2018) Biofortified crops generated by breeding, agronomy and transgenic approaches are improving the lives of millions of people around the world. *Frontiers in Nutrition* DOI: 10.3389/fnut.2018.00012; De Steur H, Demont M, Gellynck X, Stein AJ (2017) The social and economic impact of biofortification through genetic modification. *Current Opinion in Biotechnology* 44: 161-168; Paul J-Y, Harding R, Tushemereirwe W, Dale J (2018) Banana21: From gene discovery to deregulated golden bananas. *Frontiers in Plant Science* 9: DOI: 10.3389/fpls.2018.00558.

problem, and according to the World Health Organization, in 2017 there was an estimated 219 million cases of malaria and 435,000 deaths, of which 61% are children under 5 years. Further, an estimated US$3.1 billion was spent on malaria control and elimination efforts globally, with no significant progress made in global malaria incidence since 2010. Furthermore, mosquitoes are becoming increasingly resistant to pesticides and antimalarial drugs are losing efficacy[49]. There is an obvious need for research on new mosquito control methods[50], and gene drives with their potential to be relatively long-term and cost-effective can complement existing methods[51].

"(g) Magnitude of actual and potential impact of the identified issue on productive sectors and economic well-being as related to the conservation and sustainable use of biodiversity;"

Synthetic biology/biotechnology is the basis of the "bioeconomy", a broad concept with visions of addressing global challenges including food security, health, industrial restructuring, and energy security[52], and about half of the 17 UN Sustainable Development Goals[53]. Substantial investment is being made in the bioeconomy, e.g. in Europe[54], where it is expected to produce economic growth and job creation, and create value through investment in innovative research and development and commercialization. Of relevance to the objectives of the CBD, the bioeconomy is also expected to improve environmental sustainability through reduced reliance on fossil fuels and improved efficiency of processes, e.g. by use of renewable resources, recycling of waste, and more efficient (reduced land use and inputs) agriculture[55].

[49] World Health Organization (2018) World malaria report. Available at: https://www.who.int/malaria/publications/world-malaria-report-2018/report/en/.
[50] Neves MP, Drumi C (2017) Ethical implications of fighting malaria with CRISPR/Cas9. *BMJ Global Health* 2: e000396 DOI:10.1136/bmjgh-2017-000396.
[51] Nolan T, Crisanti A (2017) Using gene drives to limit the spread of Malaria. *The Scientist* https://www.the-scientist.com/features/using-gene-drives-to-limit-the-spread-of-malaria-32286.
[52] Bugge MM, Hansen T, Klitkou A (2016) What is the bioeconomy? A review of the literature. *Sustainability* 8: 691 DOI:10.3390/su8070691.
[53] See: https://www.un.org/sustainabledevelopment/sustainable-development-goals/; Spasic J, Mandic M, Djokic L, Nikodinovic-Runic J (2018) *Streptomyces* spp. in the biocatalysis toolbox. *Applied Microbiology and Biotechnology* 102: 3513-3536.
[54] See: https://ec.europa.eu/research/bioeconomy/index.cfm?pg=policy.
[55] Bugge MM, Hansen T, Klitkou A (2016) What is the bioeconomy? A review of the literature. *Sustainability* 8: 691 DOI:10.3390/su8070691; OECD (2009) The bioeconomy to 2030: Designing a policy agenda. Organization for Economic Cooperation and Development, Paris.

Current "synthetic biology" applications that are the basis of the bioeconomy are predominantly microbial (aka industrial biotechnology), for example engineered microorganisms in contained conditions for the bio-based production of chemicals such as pharmaceuticals, veterinary medicines, biofuels, food additives, fragrances[56], and enzymes for a broad range of industrial uses[57]. Engineering of microbial production strains (with or without the use of "synthetic biology approaches") is aimed at higher process efficiency, stability of supply, reduced environmental impact, and improved product quality. As an example, there is a wealth of evidence about the *actual* utility of microbial fermentation for the production of enzymes[58]. Microbially sourced enzymes have been replacing enzymes sourced from animals and plants due to multiple economic and technical advantages, as well as reduced environmental impact. Economic advantages are related to the high quantity of microbial enzymes that can be produced within a short time in a small production facility. This overcomes the limitations of plant and animal sources that typically show wide variation in yield and may only be available at certain times of the year [59]. Further advantages include reduction of transport (costs and associated environmental impacts) typically associated with animal and plant sources which need to be transported to extraction facilities[60]. Technical advantages of microbial enzyme production include ease of extraction compared to plant and animal sources, better stability, as well as the possibility to easily adapt (also with genetic manipulation) to the desired production process, and ease for scalability thus reducing production footprint compared to plant and animal sources. For example, microbial production of rennin, a milk-coagulating enzyme used in cheese manufacture, is considered a significant improvement over the earlier production method that involved extraction from one organ, the cow's stomach, and the slaughter of animals[61].

[56] OECD (2014) Emerging policy issues in synthetic biology. Organization for Economic Cooperation and Development, Paris.
[57] See e.g. Gurung N, Ray S, Bose S, Rai V (2013) A broader view: Microbial enzymes and their relevance in industries, medicine, and beyond. *BioMed Res International* 329121 DOI: 10.1155/2013/329121.
[58] Gurung N, Ray S, Bose S, Rai V (2013) A broader view: Microbial enzymes and their relevance in industries, medicine, and beyond. *BioMed Res International* 329121 DOI: 10.1155/2013/329121; Spasic J, Mandic M, Djokic L, Nikodinovic-Runic J (2018) *Streptomyces* spp. in the biocatalysis toolbox. *Applied Microbiology and Biotechnology* 102: 3513-3536.
[59] Robinson PK (2015) Enzymes: principles and biotechnological applications. *Essays in Biochemistry* 59: 1–41.
[60] Gerday C, Aittaleb M, Bentahir M, Chessa J, Claverie P, Collins T, D'Amico S, Dumont J, Garsoux G, Georlette D, Hoyoux A, Lonhienne T, Meuwis M, Feller G (2000) Cold-adapted enzymes: from fundamentals to biotechnology. *Trends in Biotechnology* 18: 103-107.
[61] Robinson PK (2015) Enzymes: principles and biotechnological applications. *Essays in Biochemistry* 59: 1–41.

In the CBD synthetic biology discussions, predictions have been made about negative impacts of bio-based production systems on the income and livelihoods of small farmers in developing countries, as a consequence of production method displacement. For example, it is hypothesized that this will be the result of synthetic biology-derived products replacing those produced by traditional or "natural" means, with high profile examples including artemisinin and vanilla/vanillin. For the latter there was an extended debate in the 2015 synthetic biology online discussions[62] that highlighted the importance of carefully considering the accuracy of information presented the CBD synthetic biology discussions, and putting the issues into proper perspective. Vanillin[63] produced by engineered yeast is a different product for a different market than vanilla which is obtained from vanilla orchid pods – it competes with other synthetic vanillin products, of which the majority have been derived from petrochemicals for decades[64]. Therefore, in contrast to the claims made, the more complicated reality appears to in fact promote the objectives of the CBD.

There is a large body of published literature demonstrating the benefits of biotechnology in agriculture[65], including environmental and economic benefits for farmers in both developing and industrial countries (discussed further in topic C below). Agricultural applications of "synthetic biology" are described in the following topics (B and C below). In the broadest sense, these generally include biotech crops with an expanded range of traits compared to those currently commercialized, and crops with engineered metabolic pathways. The potential economic impact of new agricultural products for farmers can be extrapolated from existing data demonstrating the *actual* economic benefits of biotech crops. The global status of commercialized biotech crops in 2017 reported adoption in 24 countries, of which 19 are developing countries. Further, more than 18 million farmers have adopted biotech crops, of which up to 90% are small/poor farmers[66]. The most studied biotech

[62] See http://bch.cbd.int/synbio/open-ended/discussion_2014-2016.shtml.
[63] Gallage NJ, Møller BL (2015) Vanillin–bioconversion and bioengineering of the most popular plant flavor and its de novo biosynthesis in the vanilla orchid. *Molecular Plant* 8: 40-57.
[64] Waltz E (2015) Engineers of scent. *Nature Biotechnology* 33: 329-332.
[65] See http://biotechbenefits.croplife.org/.
[66] International Service for the Acquisition of Agri-biotech Applications (2018) Global status of commercialised biotech/GM crops in 2017: Biotech crop adoption surges as economic benefits accumulate in 22 years. ISAAA Brief 53-2017.

crop is Bt cotton, which is grown by more than 15 million smallholder farmers[67]. The literature shows that in developing countries, its adoption has generated additional income for the small farm sector due to higher yields and reduced pesticide input costs, and employment for the landless rural poor who rely on the labor market for their livelihood[68]. There is also evidence for improved farmer education[69] and improved economic status for women who are often the most disadvantaged in rural societies[70]. Such studies indicate that the adoption of biotechnology/synthetic biology can contribute to improving the welfare of smallholder farmers, and the broader goals[71] of decreasing poverty and more environmentally sustainable agricultural practices.

B. New technological developments in synthetic biology since the last meeting of the Ad Hoc Technical Expert Group in December 2017, including the consideration, among other things, of concrete applications of genome editing if they relate to synthetic biology, in order to support a broad and regular horizon scanning process;

SUMMARY "Synthetic biology" applications are typically associated with improved microbial production (fermentation) processes for a range of products across different sectors (e.g. pharmaceuticals, flavors, fragrances, industrial enzymes). In applications intended for environmental release such as plants, "synthetic biology" is typically associated with "new" or "next generation" products with an expanded range of traits or more "complex" traits than previous "conventionally" genetically engineered crops (e.g. herbicide tolerance and insect resistance), or with engineered metabolic pathways for the production of a product (e.g. oil, sugar). "Old" and "new" engineered crops are developed using the same established biotech tools, but the latter reflect accumulated biological knowledge and increasingly sophisticated engineering approaches. These "new" engineered crops do not present a new challenge in terms of biosafety and they are within the scope of existing regulatory mechanisms. Recent examples are discussed

[67] Bukitbayeva S, Qaim M, Swinnen J (2016) A black (white) hole in the global spread of GM cotton. *Trends in Biotechnology* 34: 260-263.
[68] See: Vitale J, Vognan G, Vitale PP (2016) The socio-economic impacts of GM cotton in Burkina Faso: does farm structure affect how benefits are distributed? *AgBioForum* 19: 120-135, and references within; Chakraborty K (2010) The economics of BT cotton production in India – a meta analysis. *Indian Journal of Economics and Business* 9(4).
[69] Ibid.
[70] Kouser S, Abedullah, Qaim M (2017) Bt cotton and employment effects for female agricultural laborers in Pakistan. *New Biotechnology* 34: 40-46.
[71] E.g. Millennium Development Goals: http://www.unmillenniumproject.org/goals/.

in this section including genome editing and gene drives, which in our view are not synthetic biology.

The GIC prefaces its response on this topic by clarifying its view that synthetic biology is not a new scientific field or paradigm. Rather, it is an umbrella term encompassing the continuum of biotechnological development beginning with the emergence of recombinant DNA technologies in the 1970s. In the CBD synthetic biology discourse, as well as in the scientific literature, it is apparent that the term is used to refer to a heterogeneous mix of activities spanning established (and re-labelled) biotechnological methods, to more recent biotechnological innovations. Further, there is no universally acceptable definition of synthetic biology, and given the diversity of technologies and applications labelled as such it is unlikely that consensus can ever be achieved on one. The GIC believes that the way that the term "synthetic biology" is used in the CBD discussions and the scientific literature is synonymous with the CBD definition of "biotechnology"[72], and that many things labelled "synthetic biology" are simply the outcomes of modern biotechnology under a new label. Nevertheless, we will avoid making distinctions in this submission, with the exception of genome editing which we insist is not synthetic biology and should not be equated to it.

Earlier CBD submissions[73] on synthetic biology have produced extensive lists of new developments that focus on tools/techniques and methods, accompanied by overblown claims of what they have already been used to achieve. The GIC cautions against giving credence to information that is speculative, often exaggerated and potentially damning of "new technology" simply because it is or appears to be new or novel. We emphasize that a technology in and of itself does not present new issues, hazards or risks. Further, research ideas, hypotheses, concepts and the like, do not constitute "new developments" – they do not correspond to fully functional technologies that have been used to generate organisms that are or will be ready in the foreseeable future for release into the environment. The GIC continues to be concerned that the CBD synthetic biology discussions have generally started from the assumption that "new developments" pose imminent danger. This notion

[72] CBD Article 2: "*Biotechnology*" means any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use.
[73] See 2017 information submissions; online discussion https://bch.cbd.int/synbio/open-ended/discussion_2017-2018/#topic1; and AHTEG report UNEP/CBD/SYNBIO/AHTEG/2017/1/3.

has steered the debate away from more pragmatic and meaningful assessments of actual needs and problems.

The GIC has long argued that the synthetic biology discussion is only meaningful when it considers current or realistically foreseeable concrete *applications.* We support the open, transparent collection and sharing of credible scientific information, preferably obtained from peer-reviewed sources. We also welcome the limitation of this topic to "since the last meeting" of the AHTEG, and we have limited our own survey to the published literature from late 2017 to the present (in this topic, and for much of the remainder of our submission). We highlight that "recent technological developments" was a topic of the previous (2017-2018) work program that was discussed by the open-ended online forum and by the 2017 AHTEG. The list of "recent developments" in the resulting AHTEG report[74] consists of examples that are not "recent", and general statements or speculation about how technologies/techniques might result in certain outcomes.

There appears to be a general consensus in the literature that current "synthetic biology" applications include microorganisms and plants containing engineered metabolic pathways. These require the insertion of multiple genes, typically of the genes giving effect to the desired pathway in other (existing) organisms, and result in a transgenic organism (aka genetically modified organism/GMO, living modified organism/LMO). The majority of applications using engineered microorganisms (aka cell factories) are in contained conditions for the production of chemicals[75]. More recent "soil microbiome" research that may result in environmental releases of engineered microorganisms is aimed at improving nitrogen fixation in cereal crops, thereby reducing the need for fertilizer application[76]. Engineered plants may be used for the production of oils and sugars[77]. An

[74] UNEP/CBD/SYNBIO/AHTEG/2017/1/3.
[75] E.g. Ro D-K, Paradise EM, Ouellet M, Fisher KJ, Newman KL, Ndungu JM, Ho KA, Eachus RA, Ham TS, Kirby J, Chang MCY, Withers ST, Shiba Y, Sarpong R, Keasling JD (2006) Production of the antimalarial drug precursor artemisinic acid in engineered yeast. *Nature* 440: 940-943.
[76] See https://joynbio.com/.
[77] Shih PM, Liang Y, Loque D (2016) Biotechnology and synthetic biology approaches for metabolic engineering and bioenergy crops. *Plant Journal* 87: 103-117.

actual current example is oilseed rape modified for omega-3 oil content, with the first regulatory approvals obtained in 2018 for its release into the environment[78].

Other "synthetic biology" examples in plants are those involving perceived "complex" traits, which like metabolic engineering, require the introduction of multiple genes. Reported areas of research include photosynthetic efficiency (higher efficiency that could lead to reduced cultivation area), water and nutrient use efficiency (reduced impact on the environment by agriculture), pest and disease resistance (reduction of pesticide use), increased yield, and nutritional enhancements[79]. In recently reported developments in photosynthetic efficiency (which is an example of metabolic pathway engineering), engineered photorespiratory pathways in tobacco resulted in productivity increases of more than 40% in field trials[80], and an engineered "chloroplastic photorespiratory bypass" resulted in increased biomass and nitrogen content in rice plants in glasshouse and field conditions[81].

The "synthetic biology" label also appears to be broadly applied to any engineered plant that is not colloquially considered to be the result of "conventional" genetic engineering, which is also understood as the long-commercialized biotech crops with herbicide tolerance or insect resistance traits. A popular example for this discrimination is bioluminescent trees, which are developed using the same routine and well-established technology[82]. Recent proof-of-concept "transgenic" or "genetically modified" developments in plants include houseplants (pothos ivy) engineered to express a protein to detoxify the hazardous organic compounds, chloroform and benzene[83]; and

[78] http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/DIR155.
[79] Gray P, Meek S, Griffiths P, Trapani J, Small I, Vickers C, Waldby C, Wood R (2018) Synthetic Biology in Australia: An Outlook to 2030. Report for the Australian Council of Learned Academies.
[80] South PF, Cavanagh AP, Liu HW, Ort DR (2019) Synthetic glycolate metabolism pathways stimulate crop growth and productivity in the field. *Science* 363: DOI: 10.1126/science.aat9077.
[81] Shen B-R, Wang L-M, Lin X-L, Yao Z, Xu H-W, Zhu C-H, Teng H-Y, Cui L-L, Liu E-E Liu, Zhang J-J, He Z-H, Peng X-X (2019) Engineering a new chloroplastic photorespiratory bypass to increase photosynthetic efficiency and productivity in rice. *Molecular Plant* (in press DOI: 10.1016/j.molp.2018.11.013).
[82] E.g. Ow DW, De Wet JR, Helinski DR, Howell SH, Wood KV, Deluca M (1986) Transient and stable expression of the firefly luciferase gene in plant cells and transgenic plants. *Science* 234: 856-859; Science for Environment Policy (2016) Synthetic biology and biodiversity, Future Brief 15; available at http://ec.europa.eu/science-environment-policy.
[83] Zhang L, Routsong R, Strand SE (2018) Greatly enhanced removal of volatile organic carcinogens by a genetically modified houseplant, pothos ivy (*Epipremnum aureum*) expressing the mammalian cytochrome P450 2e1 gene. *Environmental Science & Technology* DOI: 10.1021/acs.est.8b04811.

engineered “containment” (sterility) traits developed in poplars for the purpose of preventing the spread of transgenic trees beyond forestry plantations[84]. More early stage research includes the development of transgenic blue roses[85]. A hypothetical application is the production of “chili” tomatoes, where scientists propose to increase the expression of capsaicinoids (the metabolites responsible for the pungency of *Capsicum* species) genes in tomatoes[86].

The microbial and plant synthetic biology (and transgenic/genetically modified) applications have been developed using established state of the art recombinant DNA tools. It is the approach used and/or *application* that may be described as “new”, and this capability reflects the accumulated knowledge and increasingly sophisticated understanding of biology and the associated possibilities for biological engineering[87]. For example, in the recent photorespiratory pathway work, the tools included the model plant tobacco, which was used due to the existence of high-efficiency transformation protocols, multigene constructs were developed using established Golden Gate cloning procedures, and standard *Agrobacterium* transformation was used. The “new” approach involved using modelling of three different photorespiratory pathways, and 17 multigene constructs with different promoter gene combinations were designed to test them[88]. In more conceptual disease resistance work, a model of the *Arabidopsis* pathogen defense network containing the key genes determining susceptibility to *Botrytis cinerea* was developed for the purpose of designing and testing a genetic defensive feedback control system[89].

[84] Klocko AL, Lu H, Magnuson A, Brunner AM, Ma C, Strauss SH (2018) Phenotypic expression and stability in a large-scale field study of genetically engineered poplars containing sexual containment transgenes. *Frontiers in Bioengineering and Biotechnology* DOI: 10.3389/fbioe.2018.00100.
[85] Ankanahalli N, Urs N, Hu Y, Li P, Yuchi Z, Chen Y, Zhang Y (2018) Cloning and expression of a nonribosomal peptide synthetase to generate blue rose. *ACS Synthetic Biology* DOI: 10.1021/acssynbio.8b00187.
[86] Naves ER, de Ávila Silva L, Sulpice R, Araújo WL, Nunes-Nesi A, Peres LPE, Zsögön A (2019) Capsaicinoids: Pungency beyond Capsicum. *Trends in Plant Science* (in press, published online https://www.cell.com/action/showPdf?pii=S1360-1385%2818%2930261-9.
[87] Raimbault B, Cointet J-P, Joly P-B (2016) Mapping the emergence of synthetic biology, *PLoS ONE* DOI: 10.1371/journal.pone.0161522.
[88] South PF, Cavanagh AP, Liu HW, Ort DR (2019) Synthetic glycolate metabolism pathways stimulate crop growth and productivity in the field. *Science* 363: DOI: 10.1126/science.aat9077.
[89] Foo M, Gherman I, Zhang P, Bates DG, Denby KJ (2018) A framework for engineering stress resilient plants using genetic feedback control and regulatory network rewiring. *ACS Synthetic Biology* 7: 1553 DOI: 10.1021/acssynbio.8b00037.

Genome editing

The GIC questions the focus on "genome editing" in the CBD synthetic biology discourse. While this term is less ambiguous than synthetic biology, it also encompasses a broad category of technologies and potential outcomes. The technologies are **enabling tools** that, like other "older" (or established) technologies, may be used in various applications. Many of the "new developments" in genome editing are aimed at clinical applications (e.g. gene therapy), which may eventually be used in other applications, including crop breeding. In crops which are one of the most foreseeable applications of genome editing, the outcomes of genome editing range from mutations, which are comparable to the outcomes of conventional breeding, to targeted gene insertions, which are comparable to transgenic crops[90]. Therefore, we do not believe that genome editing in plants represents a fundamental change from existing technologies and it should not be singled out in the CBD synthetic biology discussions. We would also add that for established technologies, extensive evidence exists regarding *actual* environmental impacts and these can be easily extrapolated and used for the evaluation of gene edited crops (see topic C below).

The GIC believes that there is misunderstanding and misinformation concerning genome editing in the CBD synthetic biology discussions. As indicated above, in our view genome editing results in two types of outcomes in plants – transgenic organisms (LMOs) and mutant organisms (not LMOs), and none of these constitute "synthetic biology". In regard to the types of mutations, to date the predominant use of genome editing in plants is for generating deletions (aka "knock-outs") that result in loss of gene function (by preventing expression of a protein). These types of mutations are considered equivalent to those which can arise via spontaneous mutations in plant genomes, and/or through the use of "conventional" (non-biotech) plant breeding tools, e.g. induced mutagenesis (irradiation or chemical)[91]. Induced mutagenesis techniques have been used since the 1950s[92] to

[90] Custers R, Casacuberta JM, Eriksson D, Sági L, Schiemann J (2019) Genetic alterations that do or do not occur naturally; Consequences for genome edited organisms in the context of regulatory oversight. *Frontiers in Bioengineering and Biotechnology* 6: DOI: 10.3389/fbioe.2018.00213.

[91] Arber W (2010) Genetic engineering compared to natural genetic variations. *New Biotechnology* 27: 517-521; Schnell J, Steele M, Bean J, Neuspiel M, Girard C, Dormann N, Peason C, Savoie A, Bourbonniérre L, Macdonald P (2015) A comparative analysis of insertional effects in genetically engineered plants: Considerations for pre-market assessment. *Transgenic Research* 24: 1-17; Strauss SH, Sax JK (2016) Ending event-based regulation of GMO crops. *Nature Biotechnology* 34: 474-477.

[92] FAO/IAEA (2011). Plant Mutation Breeding and Biotechnology. Available at: http://www.fao.org/3/a-i2388e.pdf.

develop 3283 officially released cultivars in more than 200 plant species[93]. The resulting mutations include deletions ranging in size from tens to millions of base pairs, and rearrangements that include inversions and chromosomal translocations[94]. Limitations of this approach are that large populations of mutagenized plants must be screened in order to select for the desired changes, and generations of crossing may then be needed to segregate away unwanted mutations[95]. These limitations are overcome by genome editing techniques that allow for precise targeting of genome sequences for deletions or nucleotide substitutions and reduce or avoid the need to perform several generations of backcrossing.

The 2017 AHTEG report refers specifically to "gene editing" tools that enable the "simultaneous targeting of multiple sites, or multiplexing, within a genome in one step"[96]. This also appears to be the basis for inclusion of genome editing as a synthetic biology development by the Scientific Committees advising the European Commission[97]. The ability to "multiplex" or "co-edit" is regarded as a major advantage of the genome editing technology known as CRISPR[98], and to date it has primarily been used to generate knock-outs, e.g. in bacterial genomes (e.g. *Streptomyces*[99], *E. coli*[100]) and yeast[101]. A valuable application of this approach is the generation of mutant libraries, which are

[93] FAO/IAEA Mutant Variety Database available at https://mvd.iaea.org/#!Home (accessed 16 January 2019); Podevin N, Davies HV, Hartung F, Nogue F, Casacuberta JM (2013) Site-directed nucleases: A paradigm shift in predictable, knowledge-based plant breeding. *Trends in Biotechnology* 31: 375-383.
[94] Schnell J, Steele M, Bean J, Neuspiel M, Girard C, Dormann N, Peason C, Savoie A, Bourbonniérre L, Macdonald P (2015) A comparative analysis of insertional effects in genetically engineered plants: Considerations for pre-market assessment. *Transgenic Research* 24: 1-17.
[95] Podevin N, Davies HV, Hartung F, Nogue F, Casacuberta JM (2013) Site-directed nucleases: A paradigm shift in predictable, knowledge-based plant breeding. *Trends in Biotechnology* 31: 375-383.
[96] UNEP/CBD/SYNBIO/AHTEG/2017/1/3 (page 3).
[97] SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), SCHER (Scientific Committee on Health and Environmental Risks), SCCS (Scientific Committee on Consumer Safety) (May 2015) Synthetic Biology II - Risk assessment methodologies and safety aspects, Opinion II.
[98] "CRISPR" refers to "clustered regularly interspaced short palindrome repeats". Most reported applications involve the use of CRISPR-Cas9; Cas9 refers to CRISPR-associated protein.
[99] Li L, Wei K, Zheng G, Liu X, Chen S, Jiang W, Lu Y (2018) CRISPR-Cpf1-assisted multiplex genome editing and transcriptional repression in *Streptomyces*. *Applied and Environmental Microbiology* 84:e00827-18 DOI: 10.1128/AEM.00827-18.
[100] Feng X, Zhao D, Zhang X, Ding X, Bi C (2018) CRISPR/Cas9 assisted multiplex genome editing technique in *Escherichia coli*. *Biotechnology Journal* 13: e1700604 DOI: 10.1002/biot.201700604.
[101] Guo X, Chavez A, Tung A, Chan Y, Kaas C, Yin Y, Cecchi R, Garnier SL, Kelsic ED, Schubert M, DiCarlo JE, Collins JJ, Church GM (2018) High-throughput creation and functional profiling of DNA sequence variant libraries using CRISPR–Cas9 in yeast. *Nature Biotechnology* DOI:10.1038/nbt.4147.

an essential tool for studying gene function, and in particular for discovering the role of previously uncharacterized genes and connecting them to biological pathways[102].

The use of CRISPR-based multiplex genome editing to generate knock-outs in plants has been reported, e.g. in *Arabidopsis*, rice, maize[103], sorghum[104] (enhanced nutritional quality), wheat[105], and tomato[106]. For example, in sorghum, the co-editing of a multigene family for loss of function resulted in reduced kafirin content and improved grain quality and digestibility[107]. In hybrid rice, co-editing of four genes resulted in plants that could propagate clonally through seeds, with this approach having the potential to enable the self-propagation of elite F1 hybrids in other crops[108]. In tomato, co-editing of six genes for loss of function in a wild relative resulted in the introduction of key features of domesticated tomato, including fruit size, shape, number, lycopene content, and compact plant growth[109]. Also, the simultaneous generation of point mutations involving the insertion of one or two nucleotides (for loss of function) has been reported in *Arabidopsis* and rice[110].

The types of mutations generated with these applications of genome editing can also be achieved using conventional breeding techniques, including induced mutagenesis, however as noted above these approaches result in random mutations. The possibility to target different *loci* simultaneously can speed up the breeding time due to the reduction of the number of generations needed for trait

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[102] Ibid.
[103] Borrelli VMG, Brambilla V, Rogowsky P, Marocco A, Lanubile A (2018) The enhancement of plant disease resistance using CRISPR/Cas9 technology. *Frontiers in Plant Science* 9: article 1245 DOI: 10.3389/fpls.2018.01245.
[104] Li A, Jia S, Yobi A, Ge Z, Sato SJ, Zhang C, Angelovici R, Clemente TE, Holding DR (2018) Editing of an alpha-kafirin gene family increases digestibility and protein quality in sorghum. *Plant Physiology* 177: 1425–1438.
[105] Sánchez-León S, Gil-Humanes J, Ozuna C V, Giménez MJ, Sousa C, Voytas DF, Barro F (2017) Low-gluten, nontransgenic wheat engineered with CRISPR/Cas9. *Plant Biotechnology Journal* 16: 902-910.
[106] Zsögön A, Čermák T, Naves ER, Notini MM, Edel KH, Weinl S, Freschi L, Voytas DF, Kudla J, Peres LEP (2018) De novo domestication of wild tomato using genome editing. *Nature Biotechnology* DOI: 10.1038/nbt.4272.
[107] Li A, Jia S, Yobi A, Ge Z, Sato SJ, Zhang C, Angelovici R, Clemente TE, Holding DR (2018) Editing of an alpha-kafirin gene family increases digestibility and protein quality in sorghum. *Plant Physiology* 177: 1425–1438.
[108] Wang C, Liu Q, Shen Y, Hua Y, Wang J, Lin J, Wu M, Sun T, Cheng Z, Mercier R, Wang K (2019) Clonal seeds from hybrid rice by simultaneous genome engineering of meiosis and fertilization genes. *Nature Biotechnology* DOI: 10.1038/s41487-018-0003-0.
[109] Zsögön A, Čermák T, Naves ER, Notini MM, Edel KH, Weinl S, Freschi L, Voytas DF, Kudla J, Peres LEP (2018) De novo domestication of wild tomato using genome editing. *Nature Biotechnology* DOI: 10.1038/nbt.4272.
[110] Ma X, Zhang Q, Zhu Q, Liu W, Chen Y, Qiu R, Wang B, Yang Z, Li H, Lin Y, Lin Y, Xie Y, Shen R, Chen S, Wang Z, Chen Y, Guo J, Chen L, Zhao X, Dong Z, Liu Y-G (2015) A robust CRISPR/Cas9 system for convenient, high-efficiency multiplex genome editing in monocot and dicot plants. *Molecular Plant* 8: 1274–1284.

introgression and trait pyramiding, and opens up the possibility to overcome limits of meiotic recombination in breeding lines[111]. Co-editing is considered particularly useful for targeted mutations for achieving loss of function in crops with large and highly polyploid genomes with multiple gene copies as they are not readily amenable to conventional mutagenesis techniques. For example, the use of CRISPR in wheat to simultaneously edit three homeologs of the *Ms45* gene was reported to result in male sterility[112], and targeting the multiple copies of gliadin genes showed potential for producing hypoimmunogenic (gluten) wheat[113]. The use of a different technology (Transcription activator-like effector nuclease, TALEN) was reported in sugarcane for the co-editing of more than 100 copies/alleles of one gene, the lignin biosynthetic gene *caffeic acid O-methyltransferase*[114].

An area of genome editing that rose in prominence from late 2017 is base editing for generating single point mutations, e.g. C to T or A to G conversions. The use of CRISPR-based base editing is considered to have great potential for the treatment of human diseases, since most clinically relevant mutations are point mutations[115]. In crops, base editing has been demonstrated in *Arabidopsis*, *Brassica napus*[116], rice[117], and wheat[118]. These mutations can also be achieved using conventional breeding techniques, however base editing allows for high precision in targeting specific genomic

[111] Nogué F, Mara K, Collonnier C, Casacuberta JM (2016) Genome engineering and plant breeding: impact on trait discovery and development. *Plant Cell Reports* 35: 1475-1486.
[112] Singh M, Kumar M, Albertsen MC, Young JK, Cigan AM (2018) Concurrent modifications in the three homeologs of *Ms45* gene with CRISPR-Cas9 lead to rapid generation of male sterile bread wheat (*Triticum aestivum* L.) *Plant Molecular Biology* 97: 371–383.
[113] Jouanin A, Boyd L, Visser RGF, Smulders MJM (2018) Development of wheat with hypoimmunogenic gluten obstructed by the gene editing policy in Europe. *Frontiers in Plant Science* DOI: 10.3389/fpls.2018.01523.
[114] Kannan B, Jung JH, Moxley GW, Lee S-M, Altpeter F (2018) TALEN-mediated targeted mutagenesis of more than 100 COMT copies/alleles in highly polyploid sugarcane improves saccharification efficiency without compromising biomass yield. *Plant Biotechnology Journal* 16: 856–866.
[115] See e.g. Gapinske M, Luu A, Winter J, Woods WS, Kostan KA, Shiva N, Song JS, Perez-Pinera P (2018) CRISPR-SKIP: programmable gene splicing with single base editors. *Genome Biology* 19:107 DOI: 10.1186/s13059-018-1482-5; Guo X, Chavez A, Tung A, Chan Y, Kaas C, Yin Y, Cecchi R, Garnier SL, Kelsic ED, Schubert M, DiCarlo JE, Collins JJ, Church GM (2018) High-throughput creation and functional profiling of DNA sequence variant libraries using CRISPR–Cas9 in yeast. *Nature Biotechnology* DOI:10.1038/nbt.4147.
[116] Kang B-C, Yun J-Y, Kim S-T, Shin Y, Ryu J, Choi M, Woo JW, Kim J-S (2018) Precision genome engineering through adenine base editing in plants. *Nature Plants* DOI: 10.1038/s41477-018-0178-x.
[117] Hua K, Tao X, Zhu J-K (2018) Expanding the base editing scope in rice by using Cas9 variants. *Plant Biotechnology Journal* DOI: 10.1111/pbi.12993; Li C, Zong Y, Wang Y, Jin S, Zhang D, Song Q, Zhang R, Gao C (2018) Expanded base editing in rice and wheat using a Cas9-adenosine deaminase fusion. *Genome Biology* 19:59 DOI: 10.1186/s13059-018-1443-z.
[118] Li C, Zong Y, Wang Y, Jin S, Zhang D, Song Q, Zhang R, Gao C (2018) Expanded base editing in rice and wheat using a Cas9-adenosine deaminase fusion. *Genome Biology* 19:59 DOI: 10.1186/s13059-018-1443-z.

sequences. We once again clearly state, genome editing is not synthetic biology and should not be equated to it, and mutants developed using genome editing are not LMOs.

Gene drives

As discussed above in topic A, gene drives are a major topic in the CBD synthetic biology discussions. Organisms containing engineered gene drives are developed using genome editing technologies, most commonly CRISPR. The GIC is of the view that organisms containing gene drives are LMOs that are within the scope of existing biotech regulatory mechanisms. Since 2015, proof of concept has been established for CRISPR-based gene drives in yeast (*Saccharomyces cerevisiae*), fruit flies (*Drosophila melanogaster*), and two species of mosquitoes (*Anopheles stephensi*, *Anopheles gambiae*) that are vectors of infectious human diseases[119]. More recently in July 2018, there were media reports of gene drives being tested in mammals (mice) for the first time, to manipulate coat colour. This was widely heralded as a step towards using gene drives to eradicate invasive animals such as rodents[120], however this work was not a proof of concept in a mammalian system and the research community has itself stated that they are several years away from this[121]. The report noted that many technical hurdles were encountered and much more work is needed before gene drives could be considered for population control in mammals[122].

Other *potential* applications of gene drives that have been raised in the CBD synthetic biology discussions include agriculture, e.g. by reversing pesticide and herbicide resistance in insects and weeds[123], or controlling insects that are vectors of crop diseases[124]. In a recent development, the creation of an engineered gene drive system was reported in a major worldwide pest of soft-skinned

[119] National Academies of Sciences Engineering and Medicine (2016) Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. Washington, DC: The National Academies Press. DOI: 10.17226/2340.
[120] E.g. Collins CH. Gene drive: A genetic tool that can alter – and potentially eliminate – entire species has taken a dramatic leap forward. *Scientific American* 14 September 2018. https://www.scientificamerican.com/article/gene-drive1/.
[121] Island Conservation 2017 CBD submission, available at: https://bch.cbd.int/database/record.shtml?documentid=112072.
[122] *Nature News* 06 July 2018. Controversial gene drives tested in mammals for the first time. *Nature* 559, 164 DOI: 10.1038/d41586-018-05665-1. https://www.nature.com/articles/d41586-018-05665-1.
[123] Collins JP (2018) Gene drives in our future: challenges of and opportunities for using a self-sustaining technology in pest and vector management. *BMC Proceedings* 12(Suppl 8)9 DOI: 10.1186/s12919-018-0110-4.
[124] Australian Academy of Science (2017) Discussion Paper: Synthetic gene drives in Australia – Implications of emerging technologies.

fruit crops, *Drosophila suzukii*[125]. The authors highlighted the need for further research into the fitness cost of the drive and its ability to spread, and that resistance could be a major obstacle to the utility of the gene drive[126]. As discussed at length under topic A above, claims regarding the potential applications and impacts of gene drives need to be tempered by consideration of the status and realities of technology development.

In another recent development, a CRISPR-based approach was reported as a "next generation" Sterile Insect Technology (SIT). The described technology is based on knock-out mutations, with the simultaneous disruption of genes essential for female viability and male fertility resulting in the release of eggs from which sterile males emerge. This technology is reported to not have a detrimental impact on the fitness or competitiveness of sterile males, which is an improvement on the range of classical SIT and other methods (including induced mutagenesis) that are still used for insect population control, some of which date back to the 1930s (e.g. chromosome translocations, chemosterilants, irradiation, antibiotics, and bacterial infections). The reported method therefore has the potential for improved population control compared to existing approaches[127].

C. The current state of knowledge by analysing information, including but not limited to peer-reviewed published literature, on the potential positive and negative environmental impacts, taking into account human health, cultural and socioeconomic impacts, especially with regard to the value of biodiversity to indigenous peoples and local communities, of current and near-future applications of synthetic biology, including those applications that involve organisms containing engineered gene drives, taking into account the traits and species potentially subject to release and the dynamics of their dissemination

[125] Buchman A, Marshall JM, Ostrovski D, Yang T, Akbari OS (2018) Synthetically engineered Medea gene drive system in the worldwide crop pest *Drosophila suzukii*. *Proceedings of the National Academies of Sciences USA* 115: 4725-4730.
[126] Ibid.
[127] Kandul NP, Liu J, Sanchez HM, Wu SL, Marshall JM, Akbari OS (2019) Transforming insect population control with precision guided sterile males with demonstration in flies. *Nature Communications* 10: DOI: 10.1038/s41467-018-07964-7.

SUMMARY The potential positive impacts and potential negative impacts of synthetic biology have been discussed at length as requested in several COP decisions**.** Our view is that LMOs developed using "synthetic biology" that are currently released into the environment, or will be released in the foreseeable future, do not require fundamental changes in regulatory approaches compared to LMOs developed to date, nor do they pose novel biosafety risks. A wealth of evidence exists demonstrating the positive environmental impacts of LMOs released into the environment over more than two decades. From these, predictions can be made about the potential positive impacts of LMOs developed using synthetic biology approaches.

The opportunity to improve human health, the environment and social welfare is a driver of technological development. This is evident in the examples and literature we have cited for potential and actual applications aimed at improving the sustainability and efficiency of production processes and agricultural practices. The literature also provides *credible* evidence of benefits from *actual* applications of biotechnology and strong indications about the potential benefits from products early in development[128]. As we have stated here and previously, in our view, "synthetic biology" applications in crops (organisms for which we have the most experience with releases into the environment) do not result in organisms that are fundamentally different from currently commercialized biotech crops. In the GIC's 2017 CBD synthetic biology submission[129] we elaborated on the substantial body of published evidence on the *actual* positive environmental impacts of biotech crops[130], including[131]:

- Improved soil fertility;
- Reduced chemical inputs;
- Reduced fossil fuel use;

[128] E.g. see the GIC's 2017 CBD information submission, available at: https://bch.cbd.int/database/record.shtml?documentid=112053.
[129] Available at: https://bch.cbd.int/database/record.shtml?documentid=112053.
[130] See literature compiled at: http://biotechbenefits.croplife.org/impact_areas/environmental-benefits/.
[131] E.g. recent publications: Biden S, Smyth SJ, Hudson D (2018) The economic and environmental cost of delayed GM crop adoption: The case of Australia's GM canola moratorium. *GM Crops and Food* 2: 13-20; Dively GP, Venugopal PD, Bean D, Whalen J, Holmstrom K, Kuhar TP, Doughty HB, Patton T, Cissel W, Hutchison WD (2018) Regional pest suppression associated with widespread Bt maize adoption benefits vegetable growers. *Proceedings of the National Academy of Sciences USA* 115: 3320-3325; Pellegrino L, Bedini S, Nuti M, Ercoli L (2018) Impacts of genetically engineered maize on agronomic, environmental and toxicological traits: A meta-analysis of 21 years of field data. *Nature* 8: 3113 DOI: 10.1038 /s41598-018-21284-2.

- Reduced impacts on non-target organisms;
- Area-wide pest suppression;
- Decreased CO_2 emissions;
- Increased efficiency of water use;
- Higher yields.

The potential benefits of "new" applications that have been proposed include those listed above, as well as disease and pest resistance, nitrogen use efficiency (reduced fertilizer use), improved quality (e.g. flavor, fibre quality), and improved processing characteristics[132]. Recent examples include the photosynthetic efficiency work discussed above (topic B) that is aimed at higher crop productivity (yield)[133], and biofortified crops to address micronutrient deficiencies[134].

Evidence also exists for the human health and safety, and socio-economic benefits of commercialized biotech crops[135]. The human health aspect has been focused on establishing safety, and scientific risk assessment has overwhelmingly demonstrated that these crops are as safe and nutritious as their conventional (non-biotech) counterparts for human consumption[136]. Socio-economic benefits include demonstrated income gains for farmers in both developing and industrial countries as a result of yield and production gains and cost savings[137] (discussed above in topic A).

[132] OECD (2014) Emerging policy issues in synthetic biology. Organization for Economic Cooperation and Development, Paris.
[133] South PF, Cavanagh AP, Liu HW, Ort DR (2019) Synthetic glycolate metabolism pathways stimulate crop growth and productivity in the field. *Science* 363: DOI: 10.1126/science.aat9077.
[134] Garg M, Sharma N, Sharma S, Kapoor P, Kumar A, Chunduri V, Arora P (2018) Biofortified crops generated by breeding, agronomy and transgenic approaches are improving the lives of millions of people around the world. *Frontiers in Nutrition* DOI: 10.3389/fnut.2018.00012; De Steur H, Demont M, Gellynck X, Stein AJ (2017) The social and economic impact of biofortification through genetic modification. *Current Opinion in Biotechnology* 44: 161-168; Paul J-Y, Harding R, Tushemereirwe W, Dale J (2018) Banana21: From gene discovery to deregulated golden bananas. *Frontiers in Plant Science* 9: DOI: 10.3389/fpls.2018.00558.
[135] See literature compiled at: http://biotechbenefits.croplife.org/impact_areas/environmental-benefits/.
[136] Delaney B, Goodman RE, Ladics GS (2017) Food and feed safety of genetically engineered crops. *Toxicological Sciences* 162: 361-371; Society of Toxicology Issue Statement Food and Feed Safety of Genetically Engineered Food Crops (November 2017). Available at: https://www.toxicology.org/pubs/statements/SOT_Safety_of_GE_Food_Crops_Issue_Statement_FINAL.pdf.
[137] Brookes G, Barfoot P (2018) Farm income and production impacts of using GM crop technology 1996-2016. *GM Crops and Food* 9: 59-89. See also Brookes G (2018) The farm level economic and environmental contribution of Intacta soybeans in South America: The first five years. *GM Crops and Food* 9: 140-151; Biden S, Smyth SJ, Hudson D (2018) The economic and environmental cost of delayed GM crop adoption: The case of Australia's GM canola moratorium. *GM Crops and Food* 2: 13-20.

The potential positive impacts of gene drives are discussed above under topic A, and we have focused on the most foreseeable applications of mosquito control and the strong case for potential public health benefits (see Topic A, paragraph 12 criterion (f)). There is also a strong case for proposed conservation applications of gene drives, in particular for the control of invasive species (e.g. mice and rats) on islands[138]. The reported anticipated benefits of gene drives as a rodent eradication method include species specificity, lack of toxicant use, and they are relatively humane as animals are not killed[139]. Other control methods such as mechanical traps also lack species specificity, are labour intensive, and are insufficient for eradication programs without the use of additional methods[140].

The focus on islands for eradication programs is due to their higher biodiversity compared to mainlands, and the disproportionate effect of introduced species on native wildlife evident in high rates of extinction and critically endangered species[141]. The isolated nature of islands is also considered to be an advantage for managing gene drives, particularly islands without human inhabitants, and for ground dwelling animals, however it is recognized that gene flow between geographically separate populations of the target species needs to be understood[142]. Research in

[138] Piaggio AJ, Segelbacher G, Seddon PJ, Alphey L, Bennett EL, Carlson RH, Friedman RM, Kanavy D, Phelan R, Redford KH, Rosales M, Slobodian L, Wheeler K (2017) Is it time for synthetic biology conservation? *Trends in Ecology and Evolution* 32: 97-107.

[139] Campbell KJ, Beek J, Eason CT, Glen AS, Godwin J, Gould F, Holmes ND, Howald GR, Madden FM, Ponder JB, Threadgill DW, Wegmann AS, Baxter GS (2015) The next generation of rodent eradications: Innovative technologies and tools to improve species specificity and increase their feasibility on islands. *Biological Conservation* 185: 47–58.

[140] National Academies of Sciences Engineering and Medicine (2016) Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. Washington, DC: The National Academies Press. DOI: 10.17226/2340.

[141] Ibid; Moro D, Byrne M, Kennedy M, Campbell S, Tizard M (2018) Identifying knowledge gaps for gene drive research to control invasive animal species: The next CRISPR step. *Global Ecology and Conservation* 13: e00363 DOI: 10.1016/j.gecco.2017.e00363; Jones HP, Holmes ND, Butchart SHM, Tershye BR, Kappesf PJ, Corkery I, Aguirre-Muñozh A, Armstrong DP, Bonnaud E, Burbidge AA, Campbell K, Courchamp F, Cowan PE, Cuthbert RJ, Ebbert S, Genovesi P, Howald GR, Keitt BS, Kress SW, Miskelly C, Oppel S, Poncet S, Rauzon MJ, Rocamora G, Russell JC, Samaniego-Herrerah A, Seddon PJ, Spatz DR, Towns DD, Croll DA (2016) Invasive mammal eradication on islands results in substantial conservation gains. *Proceedings of the National Academy of Science USA* 113: 4033-4038.

[142] Moro D, Byrne M, Kennedy M, Campbell S, Tizard M (2018) Identifying knowledge gaps for gene drive research to control invasive animal species: The next CRISPR step. *Global Ecology and Conservation* 13: e00363 DOI: 10.1016/j.gecco.2017.e00363; National Academies of Sciences Engineering and Medicine (2016) Gene

mammalian conservation applications of gene drives is in its infancy and a proof-of-concept of a gene drive in a mammalian system has not yet been reported, however the research community is actively identifying knowledge gaps to direct future research[143]. It is interesting to note that malaria control extends to conservation, with a proposed gene drive application the control of mosquitoes to prevent the transmission of avian malaria[144].

D. Living organisms developed thus far through new developments in synthetic biology that may fall outside the definition of living modified organisms as per the Cartagena Protocol.

SUMMARY **The GIC is of the view that all examples** of engineered organisms discussed in this submission, with the exception of mutants developed using genome editing, are LMOs as defined by and within the scope of the Cartagena Protocol. Examples that have been discussed in this context in the CBD synthetic biology discussions also include protocells and orthogonal biological systems using alternative nucleotides (xenobiology). Protocells remain non-living according to the definitions of the Cartagena Protocol and outside of its scope. For xenobiology, the technology is in the very early stages of development, but the use of synthetic nucleotides (XNA) does not exclude it from the scope of the Cartagena Protocol.

The GIC notes that previous online discussions in 2015[145] and 2017[146], and the AHTEG meetings of 2015[147] and 2017[148], considered this topic. The GIC made submissions to that work, and its views have not changed in relation to new developments – living organisms already developed or currently under research and development through techniques of "synthetic biology" are LMOs as defined by

Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. Washington, DC: The National Academies Press. DOI: 10.17226/2340.

[143] E.g. Ibid.

[144] Piaggio AJ, Segelbacher G, Seddon PJ, Alphey L, Bennett EL, Carlson RH, Friedman RM, Kanavy D, Phelan R, Redford KH, Rosales M, Slobodian L, Wheeler K (2017) Is it time for synthetic biology conservation? *Trends in Ecology and Evolution* 32: 97-107; National Academies of Sciences Engineering and Medicine (2016) Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. Washington, DC: The National Academies Press. DOI: 10.17226/2340.

[145] See https://bch.cbd.int/synbio/open-ended/discussion_2015-2016.shtml#topic2.

[146] See https://bch.cbd.int/synbio/open-ended/discussion_2017-2018/#topic3.

[147] 2015 AHTEG report: UNEP/CBD/SYNBIO/AHTEG/2015/1/3.

[148] 2017 AHTEG report: UNEP/CBD/SYNBIO/AHTEG/2017/1/3.

the Cartagena Protocol. Further, "synthetic biology" is within the scope of "biotechnology" as defined by the CBD, and "modern biotechnology" as defined by the Cartagena Protocol. **Therefore, we believe that all of the examples discussed in this submission, with the exception of mutants developed using genome editing, are LMOs per the Cartagena Protocol.** As we have noted above, we do not consider it appropriate to include genome editing in the synthetic biology discussions, and that we consider certain organisms developed with the use of genome editing to be similar to those developed using conventional (non-biotech) methods, and these are not LMOs.

A question that both AHTEGs on synthetic biology addressed was the status of protocells. The report of the AHTEG meeting of 2015 stated that "there are cases in which there may be no consensus on whether the result of a synthetic biology application is "living" or not (for example, protocells)". The AHTEG meeting of 2017 agreed that "techniques involving cell-free systems did not result in the development of living organisms" and that "to date, protocells that were capable of replicating genetic material did not exist and, as such, were not living organisms". Furthermore, should protocells capable of transferring or replicating genetic material be developed in the future, the AHTEG noted that "those might be regarded as LMOs". No new evidence has been presented since that AHTEG meeting that changes that conclusion.

Another area of basic research, which has been monitored in the CBD synthetic biology discussions, is the use of synthetic nucleotides to create orthogonal biological systems, termed xenobiology. Currently, research in this area is at an early stage and aimed at engineering microbial systems for the production of new or technically challenging biochemicals, and it is also promoted in the literature as providing new tools for studying the origin of the genetic code and life itself. A hallmark of xenobiology is the engineering and expansion of the genetic code with alternative chemical structures termed Xeno-DNA (XNA) for the purpose of increasing chemical diversity beyond the 20 canonical (naturally occurring) amino acids. A recent example, which is also one of the first applications of xenobiology in medicine, is the development of semi-synthetic interleukin-2 (IL-2) for the treatment of solid tumors, with evidence indicating the potential for reduced toxicity-associated side effects in patients[149].

[149] Synthorx 2018. Synthorx to Present Preclinical Data for THOR-707, a "Not-Alpha" IL-2 Synthorin, for the Treatment of Solid Tumors at SITC 2018. Available at: https://www.prnewswire.com/news-releases/synthorx-to-present-preclinical-data-for-thor-707-a-not-alpha-il-2-synthorin-for-the-treatment-of-solid-tumors-at-sitc-2018-300747293.html.

Our view is that current applications of xenobiology are within the scope of the Cartagena Protocol, provided that they result in a "living organism" (i.e. are "capable of transferring or replicating genetic material") as defined. The development of stably propagating *E. coli* containing synthetic nucleotides was reported for the first time in 2014[150], but the development of a higher organism for intended release into the environment remains a hypothetical application. We note that the use of synthetic nucleotides does not exclude xenobiology from the CBD definition of "genetic material", which includes "material of plant, animal, microbial or **other origin**".

[150] Malyshev DA, Dhami K, Lavergne T, Chen T, Dai N, Forster JM, Correa IR, Romesberg FE (2014) A semi-synthetic organism with an expanded genetic alphabet. *Nature* 509: 385-388. See also Zhang Y, Lamb BM, Feldman AW, Zhou AX, Lavergne T, Li L, Romesberg FE (2017) A semisynthetic organism engineered for the stable expansion of the genetic alphabet. *Proceedings of the National Academy of Sciences USA* 114: 1317-1322.