Submission of the Public Research and Regulation Initiative (PRRI) in response to NOTIFICATION No. 2018-103 inviting Parties, other Governments, relevant organizations and indigenous people and local communities to submit information and supporting documentation on the four topics from decision 14/19 and nomination of experts to participate in the Open-ended Online Forum on Synthetic Biology. - Ref.: SCBD/CP/DC/MA/MW/87791

TOPIC 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;

Aware of the very significant resources that the COP discussion on Synthetic Biology has consumed, and aware that those discussions are becoming increasingly repetitive, PRRI believes that a continuation of those discussions would only be warranted if an evidence based analysis suggests that Synthetic Biology is a New and Emerging Issue in the sense of Decision IX/29.

Before addressing the criteria laid down in Decision IX/29, first some general observations.

Evidence indicates that, despite some decisive successes, current conservation approaches are not slowing the overall rate of biodiversity loss[1] and a bigger toolbox for biodiversity conservation is fundamental.

The 2006 COP 8 Decision VIII/10[2] reflects this, introducing among the functions of SBSTTA to both:
"c) Identify innovative, efficient and state-of-the-art technologies and know-how relating to the conservation and sustainable use of biological diversity and advise on the ways and means of promoting development and/or transferring such technologies;" and
"(d) Identify new and emerging issues relating to the conservation and sustainable use of biodiversity;".

While the aim comprised of identifying and promoting know-how and technologies' positive impacts while managing and mitigating negative emerging issues, the ensuing discussions focused on possible risks of technological advances without balancing the opportunities.

The equally important task of identifying and promoting technologies and know-how relating to the conservation and sustainable use of biological diversity failed to gain significant attention in the COP discussions. PRRI urges parties and relevant stakeholders to also "identify innovative, efficient and state-of-the-art technologies and know-how relating to the conservation and sustainable use of biological diversity and advise on the ways and means of promoting development and/or transferring such technologies". Understanding and addressing real world major causes of biodiversity loss and the issues underlying these causes should be a priority.

The criteria for identifying NEI were decided in 2008, included considering new evidence of unexpected and significant impacts on biodiversity; evidence of limited tools to mitigate negative impacts on biodiversity; a the urgency of addressing the issue; work already under way by relevant organizations addressing the issue; and credible sources of information (decision IX/29, paragraphs 11 and 12) [3].

Since 2010, a group of biotechnology innovative approaches or concepts, referred as Synthetic Biology, have been a growing part of the work program as described in COP decisions in 2010[4], 2012[5], 2014[6], 2016[7] and 2018[8]. After almost a decade, parties are still reflecting whether Synthetic Biology satisfies these criteria for NEI.

PRRI understands that all criteria for a NEI must be met (including those on paragraph11) and considers each of the 7 criteria laid on paragraph 12 (decision IX/29) below in the light of the general observation above.

Criteria set out in decision IX/29, paragraph 12:

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

One obvious major call to action to reduce biodiversity loss is attention on drivers identified as major concern but underrepresented in ecological and conservation research and measures. The often-listed global core drivers of biodiversity decline are:

- Habitat destruction and degradation (man caused like conversion of forest to agricultural/pasture lands or natural causes like floods, drought, volcanoes, etc.).
- Over-exploitation (extraction, hunting, fishing etc.)
- Pollution
- Diseases
- Invasions of alien species - while some non-native species offer important cultural, economic, and environmental benefits that outweigh their negative impacts; others (e.g. rats, zebra mussels, etc.) can introduce diseases, become predators and threatens native species' existence in different ways.
- Climate change (species must adapt or move to favourable locations, changes in migratory species, emerging diseases, coral bleaching …). [9]

Applications of Synthetic biology in the field of conservation are still in early stages. However, for each of the listed main threats to biodiversity, as well as, fair sharing of costs and benefits of conservation, Synthetic biology, among other knowledge and technological improvements can be an essential component to fight natural and man-made causes of biodiversity loss. Biotechnologies like synthetic biology could save horseshoe crabs that are bled alive each year for pharmaceutical use (detection of bacterial contamination) [10] by replacing the natural compound extraction by a synthetic one [11]. Likewise, synthetic biology can replace toxic/pollutants activities with more sustainable options. In addition to contributing to pollution sensing and remediation[12] [13] [14], including the conversion of waste into energy or value-added molecules[15], etc. Synthetic biology can also address lasting threats like chytridiomycosis a fungus-caused disease provoking severe declines in the populations of amphibians globally[16] as well as emerging diseases.

Conclusion: synthetic biology is relevant to the implementation of the objectives of the Convention. Key for achieving the acknowledged and expected benefits of biotechnologies[17] is cooperation between biodiversity conservationists and biotechnologists, appropriate risk assessment and management and good governance.

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

There is no new evidence of unexpected and significant adverse effects of Synthetic Biology on biodiversity.

Here too an additional general observation. Thoughtful analyses are crucial to avoid incorrect conclusions and misguided interventions. For example, Genetically modified crops have sometimes been blamed for drops of populations of Monarch butterflies, but the decline of Monarch butterfly populations and milkweed predate the use of genetically modified crops[18] .

It is also important to recognise that synbio co-evolves with other disciplines offering improvements and new tools, such as machine learning contributions to keep dangerous DNA sequences out of malicious or careless hands[19]. SynBio approaches can also provide additional safety levels, such as genetic firewalls to improve containment [20].

(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;

There is no new evidence of unexpected and significant adverse effects or risks posed by Synthetic Biology. Living organisms developed through synthetic biology are LMOs in the sense of the Cartagena Protocol and the existing methodologies for risk assessment and management are applicable and appropriate[27]. Therefore, there is no urgency of addressing the issue/imminence of the risk.

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

Most of the advances of synthetic biology are happening in the northern hemisphere. It would be important to increase the capacity building on synthetic biology so that high diversity/developing countries can benefit from its potential to conserve biodiversity and improve social economic standards.

(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;

For the current and foreseeable applications there is no challenge for tools to limit or mitigate negative impacts on the conservation and sustainable use of biodiversity. They are sufficiently covered by the CBP RA&M and regulatory mechanisms.

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

To date the advances on SB primarily focus on using Escherichia coli and Saccharomyces cerevisiae, that are suitable for bioreactors but do not survive well in natural environment.

At the present there is no issue identified for human well-being that cannot be dealt with the RA&M approach of the CBP. There are, however, numerous potential benefits to human well-being with applications to improve environmental quality especially for the poorest populations, such as addressing vector-borne diseases, poor water quality, and unintentional poisonings [28]. Pathogens continuous to arise and adapt, infectious diseases can emerge with little notice and cause serious

damaging effects. Synbio is one of the technologies that can with further scientific attention and investment and thoughtful use help in addressing environmental and human well-being issues.

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;

Throughout history a normal consequence of the evolutionary technological development is that some options get replaced by others. Many examples of fear of loss of employment in one area, was offset by demand in another. Cases include moving from horse transportation industry to automobile, elevators operators to automatic elevators, from handlooms to powered looms in the textile industry, from the turnspit dog to mechanical roasting jacks to rotate the meat without the need for a boy, dog or goose to do the work [29] . It is possible that job destruction is likely to occur faster than society can design the appropriate responses to retrain workers or redesign educational systems[30] and develop new skills for new technologies/needs.

Some synbio applications were seen as a threat to farmers' job. Since 2014, an often cited example was the semi-synthetic synthesis of artemisinin. Artemisinin and its analogues are naturally occurring most effective antimalarial secondary metabolites. These compounds also possess activity against various types of cancer cells, schistosomiasis, and some viral diseases [31].
Malaria is a major disease in the developing world. In 2017, an estimated 219 million cases of malaria occurred worldwide, and caused some 435 000 deaths mostly children aged under 5 years [32]. Since 2002, when the World Health Organization (WHO) recommended as the first-line treatment for uncomplicated malaria the Artemisinin Combination Therapy (ACT). The global market for quality-assured artemisinin-based combination therapies (QAACTs) has expanded dramatically[32,33]. The market's reliance on a vegetal artemisinin source, with all that that confers (e.g., long production cycles dictated by growing seasons, varying crop yields, competition for cultivation acreage from other in-demand cash crops, small volume growers, an inflexible supply chain that cannot easily adjust to changes in market demand) [33], has caused supply shortfalls in some years to oversupply in others as well as dramatic price fluctuations[33][34]. A synthetic-biology route was sought to provide a more affordable, stable and reliable source for artemisinin [35] in a eco-friendly and high-quality way[36]. In 2013, this option became real but it was proposed as a threat to about 100,000 farmers who were growing the crop[37]. Beyond the ethical questions of favouring a smaller number of farmers from having to switch to planting alternative cash crops or to do a different activity at the sacrifice of many more suffering from malaria for whom the treatment might be unaffordable. Cultivated *A. annua* remains the major source of artemisinin for these life-saving antimalarial medicines[33,36] . ACTs' share of market demand is expected to grow to 47% of global antimalarial demand by 2021[33]. But other reasons might be good enough for farmers and others to be open and prepared to changes. For instance, we saw the rise and fall of several antimalarial compounds due to resistance [38][39][40] and threat of spread of artemisinin resistance is growing [32][40][41,42].

Conclusion: Synthetic Biology does not fall within the criteria for New and Emerging Issues set out in Decision IX/29.

TOPIC 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;

Genome editing is a range of molecular biology applications enabling targeted and precise modifications of the genome, based on design. It can be used in numerous ways. From a single nucleotide mutation indistinguishable from those occurring regularly in nature and similar to conventional breeding, to the insertion of a gene into an organism, resulting in a GMO. Genome editing tools can also be used to delete small stretches of DNA in the genome.

The use of genome editing tools cannot be equated to LMOs, synthetic biology, or mutagenesis - it depends on the end product.

TOPIC 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; and

See Above under Topics A and B.

TOPIC 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.

We are not aware of living organisms developed through new developments in synthetic biology that may fall outside the definition of living modified organisms as per the Cartagena Protocol.

1. Piaggio AJ, Segelbacher G, Seddon PJ, Alphey L, Bennett EL, Carlson RH, et al. Is It Time for Synthetic Biodiversity Conservation? Trends Ecol Evol [Internet] 2017;32(2):97–107. Available from: http://dx.doi.org/10.1016/j.tree.2016.10.016
2. COP 8 Decision VIII/10 [Internet]. 2006 [cited 2019 Feb 9];Available from: https://www.cbd.int/decision/cop/default.shtml?id=11024
3. COP 9 Decision IX/29 [Internet]. 2008 [cited 2019 Feb 9];Available from: https://www.cbd.int/decision/cop/?id=11672
4. COP 10 Decision X/13 [Internet]. 2010 [cited 2019 Feb 9];Available from: https://www.cbd.int/decision/cop/default.shtml?id=12279
5. COP 11 Decision XI/11 [Internet]. COP 11 Decis. XI/112012 [cited 2019 Feb 9];Available from: https://www.cbd.int/decision/cop/default.shtml?id=13172
6. COP 12 Decision XII/24 [Internet]. 2014 [cited 2019 Feb 9];Available from: https://www.cbd.int/decision/cop/default.shtml?id=13387
7. CBD/COP/DEC/XIII/17 - Synthetic Biology [Internet]. 2016 [cited 2019 Feb 9]. Available from: https://www.cbd.int/doc/decisions/cop-13/cop-13-dec-17-en.pdf
8. CBD/COP/DEC/14/19 - Synthetic Biology [Internet]. 2018 [cited 2019 Feb 9]. Available from:

http://bch.cbd.int/onlineconferences/portal_detection/lab_network.shtml.
9. Chelsea Harvey. Climate Change Is Becoming a Top Threat to Biodiversity - Scientific American [Internet]. Sci. Am.2018 [cited 2019 Feb 9];Available from: https://www.scientificamerican.com/article/climate-change-is-becoming-a-top-threat-to-biodiversity/
10. Gauvry G. Current Horseshoe Crab Harvesting Practices Cannot Support Global Demand for TAL/LAL: The Pharmaceutical and Medical Device Industries' Role in the Sustainability of Horseshoe Crabs [Internet]. In: Changing Global Perspectives on Horseshoe Crab Biology, Conservation and Management. Cham: Springer International Publishing; 2015 [cited 2019 Feb 10]. page 475–82.Available from: http://link.springer.com/10.1007/978-3-319-19542-1_27
11. Maloney T, Phelan R, Simmons N. Saving the horseshoe crab: A synthetic alternative to horseshoe crab blood for endotoxin detection. PLOS Biol [Internet] 2018 [cited 2019 Feb 10];16(10):e2006607. Available from: http://dx.plos.org/10.1371/journal.pbio.2006607
12. de Lorenzo V, Prather KL, Chen G, O'Day E, von Kameke C, Oyarzún DA, et al. The power of synthetic biology for bioproduction, remediation and pollution control. EMBO Rep [Internet] 2018;e45658. Available from: http://embor.embopress.org/lookup/doi/10.15252/embr.201745658
13. Karig DK. Cell-free synthetic biology for environmental sensing and remediation. Curr Opin Biotechnol [Internet] 2017;45:69–75. Available from: http://dx.doi.org/10.1016/j.copbio.2017.01.010
14. Schmidt CW. Synthetic biology: environmental health implications of a new field. Environ Health Perspect [Internet] 2010 [cited 2019 Feb 11];118(3):A 118-23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20194062
15. Matsakas L, Gao Q, Jansson S, Rova U, Christakopoulos P. Green conversion of municipal solid wastes into fuels and chemicals. Electron J Biotechnol [Internet] 2017 [cited 2019 Feb 11];26:69–83. Available from: https://www.sciencedirect.com/science/article/pii/S0717345817300040
16. Hanlon SJO, Rieux A, Farrer RA, Rosa GM, Waldman B, Bataille A, et al. R ES E A RC H causing global amphibian declines. 2018;627(May):621–7.
17. CONVENTION ON BIOLOGICAL DIVERSITY UNITED NATIONS 1992 [Internet]. [cited 2019 Feb 9]. Available from: https://www.cbd.int/doc/legal/cbd-en.pdf
18. Boyle J, Dalgleish H, Puzey J. Monarch butterfly and milkweed declines substantially predate the use of genetically modified crops. Proc Natl Acad Sci U S A [Internet] 2019;Available from: http://dx.doi.org/10.1101/378299
19. Reardon S. How machine learning could keep dangerous DNA out of terrorists' hands. Nat 2019 5667742 2019;
20. Torres L, Krüger A, Csibra E, Gianni E, Pinheiro VB. Synthetic biology approaches to biological containment: pre-emptively tackling potential risks. Essays Biochem [Internet] 2016;60(4):393–410. Available from: http://essays.biochemistry.org/lookup/doi/10.1042/EBC20160013
21. Pardee K, Green AA, Ferrante T, Cameron DE, Daleykeyser A, Yin P, et al. Paper-based synthetic gene networks. Cell [Internet] 2014;159(4):940–54. Available from: http://dx.doi.org/10.1016/j.cell.2014.10.004
22. Takahashi MK, Tan X, Dy AJ, Braff D, Akana RT, Furuta Y, et al. A low-cost paper-based synthetic biology platform for analyzing gut microbiota and host biomarkers. Nat Commun [Internet] 2018 [cited 2019 Feb 9];9(1):3347. Available from: http://www.nature.com/articles/s41467-018-05864-4
23. Ma D, Shen L, Wu K, Diehnelt CW, Green AA. Low-cost detection of norovirus using paper-based cell-free systems and synbody-based viral enrichment. Synth Biol [Internet] 2018 [cited 2019 Feb 9];3(1). Available from:

https://academic.oup.com/synbio/article/doi/10.1093/synbio/ysy018/5102817
24. Pardee K, Green AA, Takahashi MK, Braff D, Lambert G, Lee JW, et al. Rapid, Low-Cost Detection of Zika Virus Using Programmable Biomolecular Components. Cell [Internet] 2016;165(5):1255–66. Available from: https://doi.org/10.1016/j.cell.2016.04.059
25. Yousefi H, Ali MM, Su HM, Filipe CDM, Didar TF. Sentinel Wraps: Real-Time Monitoring of Food Contamination by Printing DNAzyme Probes on Food Packaging. ACS Nano 2018;12(4):3287–94.
26. Lu Y. Cell-free synthetic biology: Engineering in an open world. Synth Syst Biotechnol [Internet] 2017;2(1):23–7. Available from: http://dx.doi.org/10.1016/j.synbio.2017.02.003
27. ZKBS - Synthetic Biology - Synthetic Biology_2nd Interim report (2018) [Internet]. 2nd Interim Rep. Ger. Cent. Comm. Biol. Saf. June 2018 [cited 2019 Feb 10];Available from: https://www.zkbs-online.de/ZKBS/SharedDocs/Downloads/02_Allgemeine_Stellungnahmen_englisch/01_general_subjects/2nd report Synthetic Biology (2018).html?nn=11794948
28. Fernández-Niño M, Islam Z. The potential of synthetic biology for improving environmental quality and human health in developing countries. Rev la Univ Ind Santander Salud 2017;49(1):93–101.
29. wilson B. Consider the Fork: A History of How We Cook and Eat [Internet]. Pinguin; 2012. Available from: https://www.cheric.org/research/tech/periodicals/view.php?seq=1078758
30. Juma C. Innovation and Its Enemies: Why People Resist New Technologies [Internet]. Oxford University Press; 2016. Available from: http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780190467036.001.0001/acprof-9780190467036
31. Kayani WK, Kiani BH, Dilshad E, Mirza B. Biotechnological approaches for artemisinin production in Artemisia. World J Microbiol Biotechnol [Internet] 2018;34(4):1–14. Available from: http://dx.doi.org/10.1007/s11274-018-2432-9
32. WHO | This year's World malaria report at a glance. WHO [Internet] 2019 [cited 2019 Feb 10];Available from: https://www.who.int/malaria/media/world-malaria-report-2018/en/
33. World Health Organization, (Acting as the host organization for, and secretariat of U [2018]. GLOBAL MALARIA DIAGNOSTIC AND ARTEMISININ TREATMENT COMMODITIES DEMAND FORECAST [Internet]. 2018 [cited 2019 Feb 11]. Available from: https://unitaid.org/assets/Global-malaria-diagnostic-and-artemisinin-treatment-commodities-demand-forecast-2017-–-2021-Report-May-2018.pdf
34. Kung SH, Lund S, Murarka A, McPhee D, Paddon CJ. Approaches and Recent Developments for the Commercial Production of Semi-synthetic Artemisinin. Front Plant Sci [Internet] 2018 [cited 2019 Feb 11];9:87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29445390
35. Hale V, Keasling JD, Renninger N, Diagana TT. Microbially derived artemisinin: A biotechnology solution to the global problem of access to affordable antimalarial drugs. Am J Trop Med Hyg [Internet] 2007 [cited 2019 Feb 10];77(SUPPL. 6):198–202. Available from: http://www.ajtmh.org/docserver/fulltext/14761645/77/6_Suppl/0770198.pdf?expires=1549799379&id=id&accname=guest&checksum=E0F81A586D620249BCF84049BAF59F88
36. Peplow M. Synthetic biology's first malaria drug meets market resistance. Nature [Internet] 2016 [cited 2019 Feb 11];530(7591):389–90. Available from: http://www.nature.com/doifinder/10.1038/530390a
37. ETC Group. Artemisinin & Synthetic Biology-A Case Study [Internet]. 2014 [cited 2019 Feb 10]. Available from: http://www.etcgroup.org/en/issues/synthetic_biology
38. Packard RM. The Origins of Antimalarial-Drug Resistance. N Engl J Med [Internet] 2014 [cited 2019 Feb 11];371(5):397–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25075832
39. D'Alessandro U, Buttiëns H. History and importance of antimalarial drug resistance. Trop Med Int Health [Internet] 2001 [cited 2019 Feb 11];6(11):845–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11703837

40. Chookajorn T. How to combat emerging artemisinin resistance: Lessons from "The Three Little Pigs". PLoS Pathog [Internet] 2018 [cited 2019 Feb 11];14(4):e1006923. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29698516
41. WHO | Q&A on artemisinin resistance. WHO [Internet] 2018 [cited 2019 Feb 11];Available from: https://www.who.int/malaria/media/artemisinin_resistance_qa/en/
42. Djimde AA, Makanga M, Kuhen K, Hamed K. The emerging threat of artemisinin resistance in malaria: focus on artemether-lumefantrine. Expert Rev Anti Infect Ther [Internet] 2015 [cited 2019 Feb 11];13(8):1031–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26081265
43. Pye RJ, Pemberton D, Tovar C, Tubio JMC, Dun KA, Fox S, et al. A second transmissible cancer in Tasmanian devils. [cited 2019 Feb 9];Available from: www.pnas.org/cgi/doi/10.1073/pnas.1519691113
44. Stammnitz MR, Coorens THH, Gori KC, Hayes D, Fu B, Wang J, et al. The Origins and Vulnerabilities of Two Transmissible Cancers in Tasmanian Devils. Cancer Cell [Internet] 2018 [cited 2019 Feb 9];33(4):607–619.e15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29634948