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ON SYNTHETIC BIOLOGY
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SYNTHESIS OF SUBMISSIONS ON SYNTHETIC BIOLOGY

Note by the Executive Secretary

I. INTRODUCTION

1. At its fourteenth meeting, in decision 14/19 on synthetic biology, the Conference of the Parties decided to extend the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology with new terms of reference, taking into account the work on risk assessment under the Cartagena Protocol, and extended also the Open-ended Online Forum to support the work of the AHTEG.

2. In paragraph 16 the decision, the Conference of the Parties invited Parties, other Governments, relevant organizations and indigenous peoples and local communities to submit to the Executive Secretary relevant information related to paragraphs (a) to (d) of the terms of reference of the AHTEG as contained in the annex to the decision. These paragraphs provide that the AHTEG is to:

(a) Provide advice on 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 CBD/SBSTTA/22/INF/17;

(b) Take stock of new technological developments in synthetic biology since the last meeting of the Ad Hoc Technical Expert Group, 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;

(c) Undertake a review of 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, as well as the need to avoid duplication with the work on risk assessment under the Cartagena Protocol on Biosafety;

(d) Consider whether any living organism developed thus far through new developments in synthetic biology fall outside the definition of living modified organisms as per the Cartagena Protocol.

3. In response to the above-mentioned decision, the Executive Secretary issued a notification inviting Parties, other Governments, relevant organizations and indigenous peoples and local communities to submit relevant information to the intersessional process on synthetic biology.[1]

* CBD/SYNBIO/AHTEG/2019/1/1.

4. A total of 28 submissions were received by the Secretariat. Among the submissions, 17 were from Parties, 1 from a non-Party, and 10 from organizations. The original submissions are available online at https://bch.cbd.int/synbio/submissions/.

II. SYNTHESIS OF INFORMATION

5. The present document summarizes the information submitted in response to notification CBD 2018-103. When reference is made to Parties, non-Parties and organizations in this document, the summary is based on their respective submission. The sub-sections below are organized around the areas on which submissions were invited, namely paragraphs (a) to (d) of the terms of reference of the AHTEG.

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

6. In addressing this topic, the submissions followed different paths to present information. A number of submissions contained general comments as well as specific statements in relation to each of the criteria for new and emerging issues (NEIs). In some submissions only, general comments or specific statements for one or more criteria were provided, while in others information focused specifically on engineered gene drives.

1. Comments on the relationship between synthetic biology and the criteria set out in decision IX/29

7. Views related to whether synthetic biology is a NEI are polarized. One aspect in which submissions differ from one another is in the way they discussed this issue. Some argue that not all the criteria set out in decision IX/29, paragraph 12, were/should be fulfilled, others have taken the approach to indicate whether synthetic biology is a NEI, and another group has provided comments underlining the need for a robust analysis to be conducted and completed. On another submission, the need for clear guidance on how the criteria for NEI should be applied was highlighted.

8. In addition, a Party mentioned that synthetic biology is not a new and emerging issue, but an existing issue, and that focus should be placed on living organisms, components and products of synthetic biology that would not fall under the Cartagena Protocol. Another Party has indicated that most of the technologies that can be considered to fall within the definition of synthetic biology will not fulfil the criteria for NEI set in paragraph 12 of decision IX/29.

9. In relation to the text in paragraph (a) of the annex to decision 14/19, which requests the AHTEG to provide advice on the relationship between synthetic biology and the criteria in decision IX/29, building on the preliminary analysis prepared by the Secretariat (CBD/SBSTTA/22/INF/17), opinions varied regarding the usefulness of the study.

10. How to apply and/or interpret the criteria was also a topic raised in the submissions. Some submissions are of the view that, if all criteria are not met, then synthetic biology should not be considered a NEI. One submission called for guidance on how to apply the criteria and suggested that this should be discussed at the fifteenth meeting of the Conference of the Parties.

11. It was also pointed out that it is challenging, to apply these criteria in a meaningful way to an undefined term such as “synthetic biology”.

12. Other submissions have approached the issues through comments directly related to engineered gene drives. For example, an organization pointed out that it is worth noting that an engineered gene drive is an approach being considered for a variety of possible applications, and that the risks and benefits associated with each gene drive application will vary, depending on the type of modification made, the species to which it is applied, and the ecosystem and geography where the organism with the drive system

[1] Notification CBD-2018-103, dated 14 December 2018.

would be used. Therefore, the organization concluded that any assessment of gene drive application should be carried out on a case-by-case basis and broad evaluations against the suggested criteria are not possible.

13. Another organization which based its comments on gene drives pointed out that gene drives, whether they meet the definition of synthetic biology or not, do not meet the criteria for a NEI. The same submission indicated that current techniques used to obtain living modified organisms (LMOs) containing gene drives, fit the definition of "modern biotechnology" as defined in the Cartagena Protocol, and that those techniques do not use "further developments or new dimensions" of modern biotechnology.

14. Finally, a Party mentioned that regulators and decision makers may face great challenges in adequately identifying and addressing the potential positive and negative impacts of synthetic biology on biodiversity, indicating that, currently, synthetic biology belongs to cutting-edge technologies that are rapidly developing, which can lead to insufficient ability of some countries to assess the risks comprehensively and to evaluate the positive and negative effect on biodiversity conservation and utilization.

2. Comments on the criteria set out in paragraph 12 of decision IX/29

15. As mentioned above, in addition to general comments, under the present section, some submissions have provided information that was specifically linked to each of the criteria. This information is presented here below.

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

16. A Party was of the view that organisms, components and products of synthetic biology can have neutral, positive or negative effects on biodiversity, and that this must be assessed on a case-by-case basis; concluding that synthetic biology is relevant for the implementation of the objectives of the Convention and its existing programmes of work. On a similar note, an organization has indicated that synthetic biology is relevant to the implementation of the objectives of the Convention while stating that cooperation between biodiversity conservationists and biotechnologists, appropriate risk assessment and management and good governance is key for achieving the benefits of biotechnologies.

17. Another Party referred to the text of paragraph 11 of decision 14/19 on synthetic biology, which calls upon Parties and other Governments, considering the current uncertainties regarding engineered gene drives, to apply a precautionary approach in accordance with the objectives of the Convention (…).

18. The submission of an organization indicated that synthetic biology falls within the definition of "biotechnology" under the Convention and "modern biotechnology" under the Cartagena Protocol, and is therefore broadly relevant. The same organization also emphasized that its relevance towards the objectives of the Convention can only be considered in the context of specific applications that are realistically foreseeable.

19. A Party referred to engineered gene drives, indicating that potential benefits of CRISPR-Cas9-enabled gene drives to human health, agriculture, and the environment is accompanied by concern over potential negative consequences to other species and ecosystems.

20. Similarly, another Party provided examples on how engineered gene drives can, at least in theory, remove whole populations from the ecosystems or can significantly alter their genetic structure. Pointing out that they can affect the conservation of biological diversity directly (by removing or altering whole species or populations) or indirectly (e.g. by changing the relations between species), negatively (e.g. directly removing whole populations or indirectly by removing the food base of some non-target species) or positively (e.g. by elimination invasive alien species, vectors or pathogens).

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

21. Three Parties and two organizations share the view that to date, there is no evidence of unexpected and significant impacts on biodiversity resulting from synthetic biology.

22. An organization noted that the word “credible” is an important inclusion in paragraph 11(e) of decision IX/29, and it is necessary to provide balance against subjective opinions as being considered “evidence”.

23. Two Parties focused their responses under this item on engineered gene drives. One of them indicated that the modelling studies show that even very inefficient gene drives are likely to be highly invasive and practically impossible to control. The same Party mentioned that since the relations between species in an ecosystem are non-linear and complex, elimination or altering of genetic structure of a whole natural population may result in effects whose nature or magnitude will be very hard to predict. The other Party who targeted its response on gene drives, remarked that CRISPR-Cas9 system appears to be particularly prone to off-target effects.

(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

24. A Party indicated that there is no evidence that risks associated with synthetic biology organisms and products would be significantly different to those associated with organisms that occur naturally, are the product of conventional breeding techniques, those that have been generated by modern biotechnology or industrial chemical products. On a similar note, another Party has mentioned that there may be challenges from future developments in the field of synthetic biology, but for a better understanding of both the positive and negative impacts of synthetic biology organisms, there is already the experience of risk assessment and risk monitoring of LMOs as a good basis to face those challenges.

25. An organization is of the view that existing regulatory mechanisms that apply to biotechnology/modern biotechnology continue to apply to any risks presented by synthetic biology related activities and products. It also mentioned that in the absence of regulatory gaps and any credible evidence of actual impacts, there can be no urgency or imminence of risk.

26. A Party pointed out that since some of the synthetic biology developments may result in potential negative effects on biodiversity, urgency of addressing synthetic biology in the effective implementation of the Convention is high. Nonetheless, the same Party also marked that potential negative effects (if any), will most probably result from living organisms obtained by synthetic biology, which so far fall under the scope of the Cartagena Protocol. Therefore, stating that urgency would be higher for those organisms obtained by synthetic biology that do not fall under the definition of an LMO.

27. In the case of engineered gene drives, a Party has indicated that currently no effective technology to control gene drives is available, and that the magnitude of actual or potential impacts on the biodiversity is hard to predict but might be significant, at least in some cases. Thus, the Party concludes that taking the above into account, this criterion is fulfilled. Also, on the issue of engineered gene drives, another Party stated that while gene-drive modified organisms hold promise for addressing persistent challenges, the proposed applications are based on limited proof-of-concept studies.

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

28. A Party is of the view that the actual geographic coverage and potential spread, including rate of spread, are likely to be dependent on different factors, such as the genetic structure of the populations (e.g. the presence and frequency of resistance alleles), effective size and geographic spread of populations affected, reproduction times, etc. The Party also indicated that in some cases, such as mice or mosquitoes, the potential effects can be global and concludes that if the above is considered, this criterion is fulfilled.

29. Another Party indicated that organisms obtained by synthetic biology that have been released so far are LMOs, and that therefore, the actual geographic coverage and potential spread is equal to that of current LMOs.

30. An organization points out that assessing phenomena such as “actual geographic coverage and potential spread” requires having a tangible or defined product/organism as the subject of the assessment.

31. A point made by a different organization is that most of the developments on synthetic biology are happening in the northern hemisphere; and that it would be important to increase the capacity building on synthetic biology so that 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

32. In this respect, an organization indicates that they agree with the conclusion of the AHTEG that tools in use for the detection, identification and monitoring of LMOs can be applied for organisms developed through synthetic biology.

33. A Party was of the view that all current and near-future organisms to be released into the environment obtained by synthetic biology are LMOs and their safety is therefore addressed under the Cartagena Protocol. However, the same Party pointed out that in the future, fast replicating and fast-spreading LMOs (such as mosquitoes) with engineered gene drives can be released and tools to mitigate these effects are so far limited. Another Party mentioned that new strong monitoring methodology and monitoring techniques should be developed for gene drive organisms.

34. A Party and an organization share the view that there is no evidence of the absence or limited availability of tools to limit or mitigate negative impacts.

35. Reflecting on engineered gene drives, a Party indicated that different approaches to control or eliminate gene drives have been proposed but so far, none of them have proven to be effective in natural context. Therefore, in the Party’s view, the release of engineered gene drives into the environment should be considered irreversible for the time being.

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

36. A Party stated that organisms, components and products of synthetic biology can have neutral, positive or negative effects on biodiversity, highlighting that the magnitude of these potential effects cannot be predicted in a generalized manner and must be assessed on a case-by-case basis.

37. A submission from an organization provides an example on gene drive application, indicating that there is an obvious need for research on new mosquito control methods, and gene drives for health applications. Another organization points to examples of 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.

38. In relation to gene drives, a Party indicated that since no gene drives have been released into environment in a large scale, only potential impact can be considered at present. Those impacts can be both positive (e.g. elimination of pathogens, pests or vectors for important diseases, such as malaria) or negative (e.g. effects of some pollinators) and of significant magnitude.

(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

39. A Party noted that organisms, components and products of synthetic biology can have neutral, positive or negative effects on several productive sectors, such as agriculture, medical sector, in biofuel production and food sector (e.g. additives, colorants, flavourings).

40. The submission of an organization pointed out that synthetic biology/biotechnology is the basis of the “bio-economy”, a broad concept with visions of addressing global challenges, including food security, health, industrial restructuring, and energy security. In addition, another organization referred to the example of artemisinin, indicating that a synthetic biology route was sought to provide a more affordable, stable and reliable source for artemisinin.

41. In relation to engineered gene drives, a Party indicated that only potential impact can be considered when it comes to impacts on human well-being. Those impacts can be either positive (e.g. increased crop yields due to pathogens or pest elimination) or negative (e.g. effects of some pollinators) and of significant magnitude.

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

42. Under this topic, several examples of new technological developments in synthetic biology were provided through the submissions. For example, an organization pointed to examples in plants, such as those involving "complex" traits, which, like metabolic engineering, require the introduction of multiple genes. Particular reference was made to areas of research including 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. Along the same lines a submission from a Party indicated that genome editing approaches (including highly multiplexed CRISPR-based methods and MAGE) may be used for large-scale engineering of metabolic pathways and networks. However, the Party commented that the efficiency of multiplexed editing is still said to be quite low and trade-offs vis-à-vis the frequency for off-target modification activity may impede the feasibility of such approaches. Some of the specific examples provided in relation to this application in plants were that in rice, up to 21 different target genes were modified in a single step, and 35 different alpha-gliadin genes out of the 45 genes in wheat were knocked out using a multiplexed approach. To conclude, the same Party indicated the potential of genome editing for an approach called "de novo domestication", i.e. to rapidly develop crop lines from wild forms with desired properties like strong resistance towards pathogens or salt tolerance. Regarding multiplexing, an organization indicated that the techniques are in their infancy, with critical knowledge gaps and uncertainties remaining on potential unintended effects.

43. An organization mentioned that an area of genome editing that has become prominent since late 2017, is base editing for generating single point mutations, e.g. C to T or A to G conversions. The submission points out that 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. Similarly, the submission indicated that in crops, base editing has been demonstrated in Arabidopsis, rapeseed, rice, and wheat.

44. The same organization also provided information of a recent development, where the creation of an engineered gene drive system was reported in a major worldwide pest of soft-skinned fruit crops, Drosophila suzukii. The submission mentioned that the authors of the publication highlighted the need for further research into the fitness cost of the drive, and that its ability to spread and resistance could be major obstacles for the utility of the gene drive. The same submission provided another example, mentioning that a CRISPR-based technology based on knockout mutations, with the simultaneous disruption of genes essential for female viability and male fertility resulted in the release of eggs from which sterile males emerge. The submission pointed out that 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 sterile insect techniques (SIT). Similarly, a Party indicated that Precision Guided SIT (pgSIT) or similar technological developments using synthetic biology and genome editing technologies, can be used to restore habitats, preserve endangered species, and to promote the development of organisms that are more productive or more adapted to climate change in more quickly, accurately and securely ways.

45. Other examples were provided by another organization which shared that laboratory populations of mosquitoes equipped with a gene drive can be suppressed within 11 generations as per a recent publication. The same organization also provided the following examples: (a) successful use of gene drives in female mouse embryos to spread a modified gene through future generations, representing the first successful uses

of a gene drive in mammals; (b) how two molecular strategies can safeguard CRISPR gene drive experiments in the laboratory, without the concern of causing an accidental spread throughout a natural population; (c) the emergence of resistance to gene drive in a population that showed suppression of those same mosquitoes in laboratory cage experiments, indicating that this was the first documented example of selection for resistance to a synthetic gene drive, allowing important design recommendations and considerations in order to mitigate for resistance in future gene drive applications.

46. Another submission, this time from a Party, shared the following examples:

(a) Engineered insect strains for population and disease control;

(b) Engineered bacteria to fight soil erosion;

(c) Insect Allies – engineering insects to combat crop stress could be repurposed;

(d) Mammalian gene-drives are possible, but suffer from limitations not observed in insects;

(e) Computer assisted design tools for synthetic biology;

(f) Template independent enzymatic DNA synthesis;

(g) Anti-CRISPR proteins can protect cells against gene editing;

(h) Machine learning can be used to determine whether gene sequences are of natural or synthetic;

(i) Origins;

(j) CRISPR-nucleases can be engineered as biological recording devices;

(k) Engineering of CRISPR-Cas12b for human genome editing.

47. The submission from a Party provided an example of recent research in the discovery of phage-derived anti-CRISPRs, which have the potential to counteract CRISPR-mediated gene regulation and prevent genome editing. The submission mentioned that research has been published on genetic modification techniques that allow for the design of specialized organisms, creating an artificial biodiversity. Other examples provided by the same Party are: (a) the insertion of a multi-gene pathway to create a new oil profile in canola plants (DHA canola); (b) alternative genetic strategies for population suppression or replacement, for example the targeted deletion of an entire sex chromosome which has the potential to bias population sex ratios. The submission mentioned that, unlike standard CRISPR gene drives, homing is not required in such approaches for spread of the transgene and replication resistant alleles will not be generated. Therefore, the submission argued, population suppression of undesirable invasive species has now moved beyond a classic gene drive approach.

48. Another submission from an organization pointed out that there have been a number of new developments that enable research and application to address different levels of control and/or mutation of nucleic acids, e.g. CasX, Cas13, Split-TALE, Base and Epigenome-Editing including dCas9 methylation or acetylation. However, the submission noted that these new developments do not necessarily produce organisms different from LMOs.

49. Other examples of new technological developments provided by a Party are in protein therapeutics that use synthetic biology to produce and treat genetic and regulatory disorders through production of biological molecules in different biological systems, or through the correction in the production or regulation of these same biological molecules in the organisms themselves, through gene editing.

50. Another Party mentioned that gene editing is being proposed for a wide range of potential traits. On animals, the development of pigs with resistance to certain diseases and double-muscled beef cattle were highlighted. Also, in relation to genome editing, an organization indicated that suggested applications for conservation include the use of genome editing to introduce barcodes into populations, introducing adaptive traits and somatic modification.

51. An organization indicated that a recent study demonstrated that CRISPR/Cas9 systems caused extensive genetic damage including small and large DNA insertions and deletions, and complex genetic rearrangements following CRISPR/Cas9 induced DNA breaks, mentioning that the pattern of changes was variable between edited cells, highlighting the unpredictability of the process.

52. The same organization highlighted that developments in other fields, such as DNA synthesis, are opening up new genome engineering projects that involve synthesising entire genomes, such as yeast. In addition, the same submission pointed out that RNA interference (RNAi) technologies are also in development and reaching commercialization, raising concerns about potential negative effects on biological diversity and human health. It further argued that it has been established that RNAi molecules acting to modulate gene expression have off-target effects on nontarget genes, some of which may be heritable.

53. The submission of information under this topic also contained some general comments that are not linked to specific examples. For instance, a Party mentioned that not all applications of genome editing necessarily result in synthetic biology organisms, highlighting that many of the tools used in synthetic biology, including genome editing, can also be used for other non-synthetic biology applications. Another Party has pointed out that it becomes necessary to understand the complexity of the modification and the new organism functions for this classification.

54. The submission of another organization has pointed out that the use of genome editing tools cannot be equated to LMOs, synthetic biology, or mutagenesis, since it depends on the final product. A Party was also of the opinion that each application of genome editing should be considered and assessed on a case-by-case basis.

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

55. Several submissions addressed the current state of knowledge on the potential positive and negative environmental impacts of current and near future applications of synthetic biology.

56. A Party indicated cited as an example a framework that was developed by a local government institution to test the use of the existing risk assessment methodology for 30 new or future applications of modern biotechnology, including synthetic biology. The outcome of the application of this framework was that the current risk assessment method appeared to be adequate for about half of these. For the other half, the risk assessment method did either not seem to be adequate because it did not concern living organisms, or insufficient knowledge or information was available to assess risks effectively. The Party indicated that it had not been concluded that potential risks of these new or future applications cannot be assessed; however, the assessment of the potential impact is more adequate if more knowledge or data are obtained.

57. A non-Party commented that genome editing techniques, including engineered gene drives, are expected to accelerate the rate at which scientists can apply biotechnology to address medical, environmental, and agricultural challenges, mentioning that these technologies are also revolutionizing biological research, advancing our understanding of living organisms and systems, and becoming vital to powering the global economy.

58. Another Party noted that, in relation to potential positive and negative environmental impacts of applications of synthetic biology, it is important to distinguish between synthetic biology techniques undertaken in controlled, contained facilities and the environmental release of organisms derived from synthetic biology. Another Party considered that it is necessary to promote research in areas such as

modelling, establishment of scenarios and experiments performed under contained use; and to adapt the experience gained in other areas of risk assessment (i.e. management of pests and invasive alien species, LMOs, etc) to explore possible positive and negative impacts of near-future applications of synthetic biology.

59. Another submission from a Party indicated that synthetic biology raises important political, scientific, economic and social issues and gives rise to a wide public debate. The Party underlined that it is therefore essential to clarify the definition of synthetic biology since that will allow countries to put in place the appropriate legal and institutional frameworks.

60. In relation to possible impacts on socio-economic considerations, the same Party indicated that certain products derived from synthetic biology are labelled as natural products which on the Party's view, creates unfair competition. In addition, the Party underscored well-being and livelihoods of local communities as areas possibly impacted by the use of certain products of synthetic biology. Another Party pointed out that the fact that organisms containing engineered gene drives can spread long distances and across geographic regions implies that they can potentially affect communities beyond the targeted release area, which triggers concerns regarding regulation, governance, and control of organisms containing engineered gene drives.

61. A party stated that, since the last meeting of the AHTEG, there had been a few articles addressing the information requested under this topic and provided examples of publications on the subjects of emerging techniques for insect genomic modifications and innovations in genome modification in yeast and its applications to environmental issues, including bioremediation and bio-sensing.

62. On the specific issue of engineered gene drives, an organization highlighted that research is most advanced for the application of controlling human diseases spread by mosquitoes, which in their view, could be a relatively long-term and cost-effective approach that can complement existing methods. Along the same line, the same organization reported that anticipated benefits of the use of gene drives as a rodent eradication method could include species specificity, lack of toxicant use, and that they are relatively humane as animals are not killed.

63. Further, in relation to the use of gene drives for eradication programmes, the same organization indicated that the isolated nature of islands is also considered to be an advantage for managing gene drives, particularly islands without human inhabitants. They also mentioned that gene flow between geographically separate populations of the target species needs to be understood. Another example of new current and near future applications of synthetic biology provided by the same organization was related to application of gene drives for mammalian conservation, which is still in its early stages.

64. Continuing the topic of gene drives, another organization referred to recent publications discussing the lack of controllability of organisms containing engineered gene drives, indicating that the invasive behaviour of gene drives is an integral part of the strategy for self-propagating versions. The submission also provided an example on the gene drive mosquitoes designed to target and disrupt a highly conserved gene that exists in all *Anopheles* mosquito species across Africa, Asia and South America, which will limit the evolution of resistance to the gene drive construct. In this respect, the organization pointed out that targeting conserved genes has the potential to affect non-target organisms, such as other Anopheles mosquitoes via intraspecific breeding or horizontal gene transfer. Along the same lines, a Party indicated that the occurrence of resistance to gene drive applications is one of the most frequently discussed risks of this new technology.

65. Also, in relation to gene drives applications, the same organization also indicated that predictions of efficacy are limited by the lack of detailed understanding of ecological and population dynamics that would be needed to begin to anticipate their effects in wild populations. The organization mentioned that, as noted for mosquitoes, lack of baseline data on dissemination dynamics, hampers the ability to predict the spread of mosquito gene drive releases, which also applies to the ability to predict efficacy of countermeasures. The submission also suggested that countermeasures, such as biological containment, and remediation strategies, such as daisy-drives, daisy-field, daisy-quorum systems, ERACRs (Element for

the Reversal of the Autocatalytic Chain Reaction) and CHACRs (Construct Hitchhiking on the Autocatalytic Chain Reaction), remain largely theoretical and are in their infancy.

66. A Party mentioned that biosafety risks of organisms containing engineered gene drives could refer to the complete eradication of species, negative impacts on non-target populations, other organisms and biodiversity. In this context, an example was provided in relation to food chain effects, such as the loss of prey and important food sources for higher trophic levels. The Party concluded that depending on the specific application, effects on predators, prey species, competitors or complex ecological functions may occur.

67. The submission of a Party underlined that science is still in the initial phase of research with gene drives and additional research it is necessary to inform an assessment of the potential positive and negative environmental impacts.

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

68. A number of submissions described examples of LMOs developed through new developments and provided views on whether or not these may fall outside the definition of living modified organism as per the Cartagena Protocol.

69. In a Party's view, in the definition of an LMO as per the Cartagena Protocol, the use of *in vitro* nucleic acid techniques is not limited to only DNA as genetic material, and, therefore, the Party argued that living organisms that are modified to contain other genetic material than DNA (such as XNA) for replication, would also fall under the definition of an LMO. The same Party further stated that examples of living organisms that fall outside the definition of LMOs seem limited to living organisms that do not contain genetic material that can be transferred or replicated (i.e. some living protocells that are still in an early state of research).

70. In relation also to protocells, an organization and another Party are of the view that protocells remain non-living according to the definitions of the Cartagena Protocol and outside of its scope. This organization has also indicated that 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.

71. A Party shared that a recent study demonstrated the creation of virus-like entities consisting of computationally designed icosahedral protein assemblies capable of packaging their own full-length mRNA genomes. The submission mentioned that those assemblies do not have all functions required for a complete viral life cycle and are not capable of transferring or replicating their genetic material; thus, they cannot be considered living organisms. The Party concluded indicating that similar non-biological synthetic assemblies might be developed in the near future, which will be capable to enter and replicate inside cells and be even more similar to naturally occurring viruses.

72. Other submissions (six Parties and one organization), indicated that they are not aware of any living organisms developed through synthetic biology that could not be considered an LMO. On the other hand, another Party referred to the case of living organisms generated by multiplexed DNA free ZFN/TALEN/MN applications, which can be considered synthetic biology and outside the Cartagena Protocol.
