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AD HOC TECHNICAL EXPERT GROUP ON SYNTHETIC BIOLOGY
Montreal, Canada, 4-7 June 2019
Item 3 of the provisional agenda*

SYNTHESIS OF DISCUSSIONS OF THE ONLINE FORUM ON SYNTHETIC BIOLOGY

Note by the Executive Secretary

I. INTRODUCTION

1. At its fourteenth meeting, in decision 14/19, 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 the Open-ended Online Forum on Synthetic Biology to support the work of the AHTEG.

2. Based on the above, the Open-ended Online Forum on Synthetic Biology was convened from 4 to 31 March 2019. The total number of participants registered for the Forum was 400. A total of 109 participants were active, and 338 interventions were made. Out of this total, 188 interventions were made by Parties, 5 by non-Parties, 141 by organizations and 4 by representatives of indigenous peoples and local communities.

3. To give effect to decision 14/19, seven topics were identified for discussion under the Forum as follows:

(a) Topic 1: New technological developments in synthetic biology since the last meeting of the Ad Hoc Technical Expert Group;

(b) Topic 2: Recommend options for carrying out the regular horizon scanning, monitoring and assessing of developments referred to in paragraph 3 of decision 14/19;

(c) Topic 3: Review of the current state of knowledge on the potential positive and negative environmental impacts of current and near-future applications of synthetic biology, including those applications that involve organisms containing engineered gene drives;

(d) Topic 4: Possible impacts of synthetic biology applications that are in early stages of research and development on the three objectives of the Convention;

(e) Topic 5: 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;

(f) Topic 6: Sharing of experiences on detection, identification and monitoring of organisms, components and products of synthetic biology;

(g) Topic 7: Relationship between synthetic biology and the criteria set out in decision IX/29.

4. The following table shows a breakdown of the interventions per topic:

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

Topic number	Number of interventions	Number of participants who made interventions
1	71	57
2	36	35
3	34	33
4	74	55
5	45	39
6	18	17
7	60	51

5. This Forum was co-moderated by Mr. Casper Linnestad from Norway and Ms. Maria de Lourdes Torres from Ecuador.

6. The present document provides a summary of the views shared through the Online Forum. For a full account of all views, it is recommended to refer to the original online interventions through the Biosafety Clearing-House (https://bch.cbd.int/synbio/open-ended/discussion/). In addition to the summaries of the seven topics, the links and references provided by various Forum participants as additional sources of information are included in document CBD/SYNBIO/AHTEG/2019/INF/3, which contains a list of references on synthetic biology.

II. SUMMARY OF INTERVENTIONS

Topic 1. **New technological developments in synthetic biology since the last meeting of the Ad Hoc Technical Expert Group**

7. This discussion focused on taking stock of new technological developments in synthetic biology since the last meeting of the AHTEG in 2017.

8. To facilitate discussion under this topic, the moderator suggested the following guiding questions:

(a) Which concrete applications of genome editing related to synthetic biology have been made recently?

(b) What new developments are known—related to the synthesis of whole genomes and chromosomes—that could have a real impact on biodiversity?

(c) Can we report on the progress of engineered gene drives in sexually reproducing organisms? Do we know about new applications of this technology?

9. Views diverged on whether new technological developments since 2017 were related to changes in technology or related to its application (i.e. genetic changes to crops through pollen).[1]

10. In relation to this topic, and in an attempt to respond to the questions suggested by the moderator, participants provided the following examples:

(a) Evidence that gene editing can be used for fast and efficient domestication of wild plants;[2]

(b) Creation of yeast with altered chromosome number;[2]

(c) Development of synthetic nucleocapsids that can package their own RNA genome;[3]

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[1] Cohen, 2019, Corn and other important crops can now be gene edited by pollen carrying CRISPR, *Science News*, doi:10.1126/science.aax2207.

[2] Li et al., Domestication of wild tomato is accelerated by genome editing, *Nature Biotechnology* 36, 1160-1163.

[2] Shao et al., Creating a functional single-chromosome yeast, *Nature* 560 (7718), 331-335.
South et al., Synthetic glycolate metabolism pathways stimulate crop growth and productivity in the field, *Science* 363 (6422), eaat9077.

[3] Butterfield et al., Evolution of a designed protein assembly encapsulating its own RNA genome, *Nature* 552 (7685), 415-420.

(d) Gene drive system in mammals;[4]

(e) Efficient gene drive that spreads rapidly in a population of caged mosquitoes;[5]

(f) New suggested gene drive applications including combatting fall army worm and *Bactrocera dorsalis* pests in sub-Saharan Africa;[6]

(g) Engineering photosynthesis;[7]

(h) The genome project-write (GP-write);[8]

(i) Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments;[9]

(j) Building living systems from scratch using chemical biology and nanotechnology tools;[10]

(k) Cell-free synthetic biology;

(l) Design of a synthetic gene to produce a new synthetic protein in the endosperm of sorghum;[11]

(m) Production of antivenoms;[12]

(n) Multiplexed CRISPR-based methods, genetic delivery systems;

(o) Transient expression;

(p) The application of synthetically engineered "biologicals" (microbes) to agriculture;

(q) Genetic code based on eight nucleotides (Hachimoji DNA);[13]

(r) Genetically modified virus applications in agriculture, including those that are transmitted by insects (HEGAAs);

(s) Xenobiological developments.

11. In relation to genetically modified viruses, a participant further elaborated indicating that environmental release is already ongoing,[14] and highlighted that viruses have potentially elevated propagation characteristics compared, for example, to genetically modified plants, and therefore need adequate scrutiny. In relation to xenobiological synthetic biology applications, the participant mentioned that these applications are further advancing and aim to expand the framework of natural chemistries

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[4] Grunwald et al., Super-Mendelian inheritance mediated by CRISPR–Cas9 in the female mouse germline, *Nature* 566 (7742), 105-109.

[5] Kyrou et al., A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged Anopheles gambiae mosquitoes, *Nature Biotechnology* 36, 1062-1066 https://doi.org/10.1038/nbt.4245

[6] Ogaugwu et al., (2019) CRISPR in Sub- Saharan Africa: Applications and Education. *Trends in Biotechnology*, Vol. 37, No. 3.

[7] South et al, Synthetic glycolate metabolism pathways stimulate crop growth and productivity in the field. *Science* Vol. 363, Issue 6422, eaat9077. Realizing Increased Photosynthetic Efficiency: https://ripe.illinois.edu/

Shen et al., Engineering a New Chloroplastic Photorespiratory Bypass to Increase Photosynthetic Efficiency and Productivity in Rice. *Molecular Plant* 12, 199-214, February 2019.

[8] Centre of Excellence for Engineering Biology, https://engineeringbiologycenter.org/

[9] Noyce, R, Lederman, S., & Evans, D., 2018, Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments, *PLoS ONE* 13(1): e0188453, https://doi.org/10.1371/journal.pone.0188453

[10] Build-A-Cell, http://buildacell.io/

[11] Liu et al., 2019, Increasing protein content and digestibility in sorghum grain with a synthetic biology approach.

[12] Parreño et al., 2018, A synthetic biology approach for consistent production of plant-made recombinant polyclonal antibodies against snake venom toxins.

[13] S. Hoshika et al., "Hachimoji DNA and RNA: A genetic system with eight building blocks," *Science*, 363:884–87, 2019.

[14] Southern Gardens Citrus Nursery, LLC Permit to release genetically modified citrus tristeza virus, United States Department of Agriculture, May 2018, https://www.aphis.usda.gov/brs/aphisdocs/17_044101r_CTV_dEIS.pdf

within living cells through the incorporation of non-natural building blocks,[15] indicating that the degradability of non-natural building blocks in the environment needs to be assessed.

12. The use of CRISPR to target RNA was mentioned by a participant, who indicated that changes in RNA are temporary and quite different compared to permanent changes caused by DNA.

13. Some interventions pointed to the ongoing discussions on the use of synthetic biology in biodiversity conservation. In this respect, a participant stated that, apart from the limited experience of the possible impacts from genetic alteration of wildlife, other issues to be considered in this respect are: long-term effects, focus on symptomatic problem solving instead of remedying the causes, as well as specific circumstances of indigenous peoples and local communities.

14. It was also mentioned that the field of synthetic biology is moving towards increasingly automated high-throughput systems for strain engineering, noting the concept of the bio-foundry,[16] whereby automation, software, machine learning, and metrology are being applied to the synthetic biology design cycle. Views were also polarized on when a new technological development should be considered as such, with some participants indicating that some ideas might never come to fruition along the developmental pathway, while others pointed out that it might be important to also discuss expected developments that have not yet materialized, suggesting that it may also be useful to identify trends in new developments instead of only focusing on actual developments (i.e. trend towards moving away from engineering of crops and focusing instead on re-engineering ecosystems).

15. Some interventions have noted that applications of synthetic biology that result in the production of LMOs should be excluded from this discussion under the Convention, since they are covered by the Cartagena Protocol.

Topic 2: Recommend options for carrying out the regular horizon scanning, monitoring and assessing of developments referred to in paragraph 3 of decision 14/19

16. In decision 14/19, paragraph 3, the Conference of the Parties agreed that regular horizon scanning, monitoring and assessing of the most recent technological developments is needed for reviewing the information regarding the potential positive and potential negative impacts of synthetic biology vis-à-vis the three objectives of the Convention.

17. To facilitate discussion under this topic, the moderator suggested the following guiding points and questions:

(a) What are suitable steps in a horizon scanning process?

(b) Cost-effective and effective mechanisms are always preferable;

(c) How to secure input from relevant sources in a timely manner?

18. The information provided by the Forum participants is synthesized as follows:

1. Steps in the horizon scanning process

19. The Forum participants provided information and examples on how the process of regular horizon scanning could be done. Some participants provided specific step-by-step options for the process, others provided more general comments on points to consider when planning for the horizon scanning, and others contributed with specific examples of similar processes that have been carried out by other organizations.

20. The following steps were suggested in the Forum for carrying out the horizon scanning:

1(a) Information gathering

[15] Diwo and Budisa, 2018, Alternative biochemistries for alien life: basic concepts and requirements for the design of a robust biocontainment system in genetic isolation., Genes, 10(1), DOI: 10.3390/genes10010017.

[16] London DNA Foundry, http://www.londondnafoundry.co.uk/foundry

1(b) Synthesis and analysis of information

1(c) Review and analysis of the outcomes

1(d) Decision-making

21. For each of the above-mentioned steps, participants provided their views on what should/could be covered and how each step could be carried out. Views from participants diverged sometimes on the steps, the content, the scope and methods to carry out the scanning process.

1(a) Information gathering

22. Some participants suggested that the collection of relevant information for this process could be done through review of scientific publications, technology surveillance reports, participation in related congresses, workshops and activities (i.e. iGEM competition), networking with key actors (i.e. the Biological Weapons Convention, the Technology Facilitation Mechanism at the United Nations Department of Economic and Social Affairs, the United Nations Commission on Science and Technology for Development at UNCTAD, and UNEP, among others), contact with scientists working in this field, online surveys, calls for submission of information from Parties and observers, Online Forum, frequent review of the registration of intellectual property rights, such as patent databases, among others.

23. A participant underlined that the process should not rely only on published literature due to the time lag between the actual research and publication, indicating that it may not provide a comprehensive view of the developments, and therefore underlined the importance of reaching out to research institutions during this process.

24. Some participants also pointed out that prioritization in the process of information gathering was of paramount importance to ensure that the information to be collected is relevant to the objectives of the Convention. Participant's views diverged on the scope of the horizon scanning, with some highlighting the need for the process to capture technologies that are emerging and not only recent developments, with the intention to make it a proactive rather than a reactive process; while others indicated that information concerning fundamental research and early research may not be as useful as information on realistically foreseeable applications that are relevant to the Convention on Biological Diversity.

25. In relation to tools that could facilitate the information gathering process, the following suggestions were provided by participants:

(a) Online survey launched by the Secretariat of the Convention on Biological Diversity to Governments, research institutions and organizations, among others;

(b) Dedicated space on the clearing-house for Parties, other Governments, organizations, indigenous peoples and local communities and other stakeholders to share information on a rolling basis;

(c) SCBD notification requesting information;

(d) SCBD Online Forum;

(e) Participation in related activities (such as workshops, symposiums, international meetings);

(f) Videoconferences;

(g) RSS or Feedly alerts from specialized journals or preprints.

26. In relation to who could be responsible for carrying out the information gathering, some participants were of the view that the Secretariat of the Convention should do it. In this respect, a participant shared the view that it would be difficult for the Secretariat of the Convention to manage all the information (for example, of publications, research institutes globally, workshops) considering the high volume of material that could be generated through this process. The participant provided the example of considering publications, indicating that a simple search of "synthetic biology" "since 2018" in Google

Scholar produced approximately 42,100 results. Other participants have suggested that the work could be done by the Secretariat of the Convention in conjunction with consultants.

1(b) Synthesis and analysis of information

27. Participants also referred to the synthesis of information once data is available. Some participants suggested that the Secretariat of the Convention could present this synthesis through an annual review paper or through a new CBD technical series on this issue.

28. It was mentioned that screening of the information to focus on what is relevant for the objectives of the Conventions is very important. An intervention indicated that in relation to the quality, relevance, and focus, of the information, an approach could be that each Party should first submit their information to their local scientific societies for evaluation, before responding to calls from the Secretariat of the Convention. The participant noted that the preliminary vetting by national scientific bodies can significantly limit the amount of material that will be shared.

1(c) Review and analysis of the outcomes

29. Some participants suggested that the synthesis of information (output) could be managed as per the existing CBD processes (i.e. the Secretariat of the Convention processes and summarizes the information and submits it to the Subsidiary Body on Scientific, Technical and Technological Advice or the Conference of the Parties. Based on this, some participants have outlined the process as follows:

(a) Submission of information to an AHTEG and ongoing online forums and/or to a standing working group on synthetic biology;

(b) Submission of outputs from the AHTEG or the Working Group to the Subsidiary Body on Scientific, Technical and Technological Advice;

(c) A recommendation of the Subsidiary Body on Scientific, Technical and Technological Advice to the Conference of the Parties.

30. In relation to the AHTEG, some participants have indicated that its involvement in a permanent process may imply that a permanent AHTEG is needed. Some interventions have also pointed to the need for resources for this purpose.

31. It was also pointed out that, while the open-ended Online Forum and AHTEG discussions are good tools towards assessment, their format is limited and, in the case of the AHTEG, need to be reauthorized from one meeting of the Conference of the Parties to the next. Another limitation that was noted is that these processes (AHTEG and online discussions) are carried out only in English. An intervention suggested that establishing a standing working group under the Convention or establishing a work stream on synthetic biology would be preferable.

1(d) Decision-making

32. The importance of what happens with the result of the horizon scanning process was acknowledged. A participant suggested that there should be a clear procedure to ensure that the information that is collected by a horizon scanning process is reported back to Parties in a timely manner.

33. Some interventions have suggested that, according to CBD processes, the Subsidiary Body on Scientific, Technical and Technological Advice should receive the result of the horizon scanning process and prepare a draft decision for the Conference of the Parties.

34. Some participants have also mentioned that, as per the cycle of CBD intersessional periods, the process will take place over a period of two years.

2. Cost-effectiveness

35. In relation to the cost-effectiveness of the horizon scanning process, some participants indicated that using some of the existing SCBD tools (i.e. online forums, BCH) and processes (Subsidiary Body on

Scientific, Technical and Technological Advice, Conference of the Parties) could be very useful towards this end.

36. One intervention indicated that requesting Parties, other Governments and relevant stakeholders to provide information to the Secretariat will result in a relatively inexpensive process that will not require a lengthy scan of published literature, while another intervention noted that requests for information are not always addressed by all from whom the information is being requested, which could then imply information gaps.

37. Participants have also pointed to the cost-effectiveness in building on the work done by others, considering that some participants have provided examples of horizon scanning or technology assessment processes.

3. Usefulness of the process and general comments

38. An intervention noted that, for the horizon scanning to be useful, its focus should not be limited to listing new technological developments. The participant indicated that the horizon scanning should also enable the identification of emerging trends and clusters of technological development that require particular governance. Similarly, a participant indicated that the horizon scanning should also include information on applications and uses of biotechnology to get a comprehensive idea of actual and potential impacts.

39. A suggestion made with a view to streamlining the process was to identify in advance the list of organizations and actors that could be contacted for information gathering purposes, and those actors could be given sufficient time to produce their inputs and network with other organizations or groups to avoid duplication of efforts and redundancy in the information that is to be provided.

40. The importance of information prioritization was underlined. A participant indicated that information could be prioritized based on risk relevance in the near term (<5 years), medium-term (5-10 years), and longer-term (>10 years).

41. A comment was also made highlighting the importance of ensuring that horizon scanning engages a wide range of stakeholders in countries around the world, and anticipates how different stakeholders may be impacted by, and can feed into the design of, emerging synthetic biology developments.

Topic 3: Review of the current state of knowledge on the potential positive and negative environmental impacts of current and near-future applications of synthetic biology, including those applications that involve organisms containing engineered gene drives

42. Discussion on this topic focused on undertaking 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 of current and near-future applications of synthetic biology, including those applications that involve organisms containing engineered gene drives. The discussion also considered human health, cultural and socioeconomic impacts, especially with regard to the value of biodiversity to indigenous peoples and local communities.

43. Participants were asked to share as much information as possible, including articles, and other materials.

44. The following guiding points and questions were suggested by the moderator:

(a) How do we get the “right picture”, the current state of knowledge?

(b) Probably, there are mixed views on what is the “right picture”.

(c) How to obtain an influx of relevant information from a variety of sources?

45. The interventions showed how participants looked at this topic from different perspectives. In some of the comments, the link between this topic and topics 1, 2 and 4 was highlighted.

46. An intervention pointed out that review of the current state of knowledge could be seen as the starting point for the horizon scanning, while other indicated that the horizon scanning will provide the current state of knowledge. It was suggested that, to address the potential positive and negative environmental impacts of current and near-future applications of synthetic biology, the information provided in the report of the AHTEG held in 2015 (UNEP/CBD/SYNBIO/AHTEG/2015/1/3, pp. 6-10) could be a useful starting point.

47. A participant indicated that to look only at the current state of knowledge is a limitation that could be costly for biodiversity and human health and pointed out the importance of considering medium- and long-term applications of synthetic biology.

48. Participants also had different views in respect to the information available. Some noted that there is not enough scientific information on the beneficial and negative effects associated with the use of synthetic biology, and that gaps in knowledge indicate that there are limits to the current knowledge relevant to the issue at hand. Others were of the view that the current state of knowledge of positive and negative effects of synthetic biology is similar to that in 2017, when very few, if any, synthetic biology organisms had been released into the environment (the last meeting of the AHTEG was in December 2017).

49. It was also noted that to reflect the current state of knowledge, there needs to be an understanding of what information is missing to identify the knowledge gaps when attempting to perform risk and impact assessments. A participant further mentioned that a wider societal perspective and discussion of technology assessment approaches that go beyond mere risk assessment are needed in order to agree on thresholds, necessities, acceptable uncertainties and common goals.

50. An intervention indicated that understanding, predicting and controlling such a complex phenomenon as biodiversity dynamics is still in its infancy, noting that additional efforts are needed to develop computer modelling tools for this purpose, which are still absent.

51. In relation to the potential effects from organisms containing engineered gene drives, the participants opinions were also polarized. Some were of the view that there is not enough knowledge on the possible effects (i.e. alter wild populations, non-target species) or on how these organisms will perform under natural conditions, indicating that, therefore, all the different scenarios along the line will need to be understood and assessed for available data and knowledge. On the other hand, others were of the view that biosafety risks posed by these organisms may be similar to those of other LMOs and noted that scientists and regulators have kept the necessary caution and indicated that ways for better controlling the technique are being developed so that there is greater understanding and control to limit undesired consequences.

52. In relation to risks associated with the complete eradication of species and negative impacts on non-target populations, participants opinions also varied, with some highlighting examples, such as effects on the food chain (loss of prey and important food sources for higher trophic levels), while others indicated that there is no evidence that removal of the species could have an impact on the food chain.

53. One participant mentioned that in relation to potential synthetic biology applications for conservation and environmental management purposes it would be good to differentiate between potential risks that would be unique to synthetic biology approaches, from those that would be incurred irrespective of the mode of management being employed. Another participant pointed out that for gene drives that suppress a population (i.e. gene drive to eliminate an invasive rodent from an oceanic island and to reduce populations of malaria-transmitting mosquitoes), it will be possible to refer to the ecological impacts of reductions caused by chemical control.

Topic 4: Possible impacts of synthetic biology applications that are in early stages of research and development on the three objectives of the Convention

54. Considering that organisms, components and products of synthetic biology could have positive and negative impacts on the conservation and sustainable use of biological diversity, the aim of discussions under this topic was to share evidence or information about actual or potential impacts.

55. The moderator proposed the following guiding questions:

(a) What information exists related to organisms containing engineered gene drives, in the light of the impacts that such organisms might have on the conservation and sustainable use of biological diversity?

(b) Can we envisage positive or negative impacts of the use of organisms, components and products of synthetic biology? Is there any evidence that support these impacts?

56. Participants considered the impact of synthetic biology on the three objectives of the Convention from different angles. Some focused on how synthetic biology could affect biodiversity conservation and sustainable use through impacting the organisms in nature (i.e. escape of a gene driver that aims to eliminate certain pests may also eliminate other wild related species), and the others focused on fair and equitable sharing of the benefits arising out of the utilization of genetic resources under the lenses of digital sequence information.

57. Some interventions noted that impacts of synthetic biology should be considered on a case-by-case basis, and other interventions indicated that, thus far, there is no evidence of current impacts.

58. Some examples of synthetic biology applications that are in early stages of research and development that could have a potential impact on the objectives of the Convention are:

(a) Manufacturing of Cyanobacteria (i.e. engineered for the photosynthetic production of fuels and fine chemicals);

(b) Applications of nitrogen fixing gene-edited bacteria and gene-edited bacteria/viruses in agriculture and for biological controls;

(c) Protocells (potential toxicity);

(d) Xenobiology;

(e) Applications to produce non-native nucleotides and amino acids inside the cell (novel engineered synthetic pathways);

(f) Development of synthetic virus-like assemblies;

(g) Applications for bioremediation or biodegradation;

(h) Applications to reduce of plastic waste;

(i) Applications to engineer microbes that can excrete compounds that mimic valuable substances;

(j) Gene drive applications (i.e. those directly aiming at conservation objectives and those that could have indirect impacts on conservation).

59. In relation to gene drives, a participant noted that there are many types of drives that differ in their structure, mode of action, the potential target species and the potential receiving environments. The participant pointed out that, based on this, there could be multiple scenarios which could lead to different results and impacts. The intervention further noted that much of the concern about gene drives is due to the possibility of spread beyond the point of release (raising governance issues when borders can be crossed), while highlighting that this is not a general property of all gene drives. The participant commented that, in some circumstances, spread may be considered a useful property, while, in other circumstances, it would be undesirable.

60. Another participant indicated that since there is no existing information on impacts on the conservation and sustainable use of biological diversity from organisms containing engineered gene drives, information related to environmental impacts of invasive species, biological control agents, applications of the sterile insect techniques to suppress mosquitoes, or from experience with insects genetically modified to suppress populations may be relevant. The intervention also stated that experience obtained from the use

of LMOs and their products can be drawn on, indicating that the same positive and negative effects may be envisaged by organisms, components and products of synthetic biology.

61. Yet another participant indicated that, if a gene drive is designed to replace other control measures, the environmental effects of this substitution may be significant. The participant also noted that balancing the local or regional extinction of a species against the benefits of disease control requires careful consideration of social, cultural and ethical factors together with the health benefits.

62. The importance of distinguishing between activities in controlled, contained facilities and the environmental release of organisms derived from synthetic biology was also regarded as important in discussing potential positive and negative impacts of synthetic biology, it is important.

63. It was noted that initially synthetic biology may be restricted to microorganisms which will be largely grown in bioreactors with minimal environmental exposure and impact, indicating that if these microorganisms are released, then the impacts become harder to assess as there has been no in vivo experience of their environmental interactions. An intervention provided the example of alien species which have usually been studied in their countries of origin, pointing that there will be no such experience with synthetic organisms and some will not have conventional counterparts to act as comparators. This participant concludes that impacts will depend on environmental studies with surrogates and surrogate comparators to determine relative fitness characteristics, initially in environmental simulations.

64. Another participant pointed out that it is important to contextualize the potential impacts (positive or negative) on biological diversity with appropriate comparators. The participant provided the example of malaria eradication activities, highlighting that these include the use of broad-spectrum insecticide and habitat modification which are likely to have significant impacts on biodiversity.

65. One participant's statement indicated that synthetic biology is allowing us to solve some significant environmental issues, including conservation issues, but we will have to find ways to transition to these types of technologies so that livelihoods can be replaced.

66. Some participants were of the view that in several cases, the benefits of releasing biological products made from synthetic biology might outperform the risks.

67. The need to explore multiple approaches in situations where there is concern about ecosystem-level effects from suppressing the population of a species was pointed out, and a participant indicated that in this respect "replacement drives" may be a preferred approach.

68. A participant focusing on potential impacts from genome editing and living organisms containing engineered gene drives indicated that with regard to genome editing techniques, there is accumulating evidence of unintended molecular effects, with implications for biological diversity and human health (i.e. CRISPR/Cas9 system was recently demonstrated to induce complex genetic rearrangements[17]), while another participant noted that an off-target effect per se is not necessarily a negative impact in itself, and that it is the consequence and the likelihood of the off-target effect being realized that should be assessed to determine the potential to cause harm.

69. Some participants mentioned that while gene editing is one of the many tools used in synthetic biology, not every application of gene editing result in a synthetic biology organism, thus highlighting that it is the outcome, not the tools used, that determines whether or not a particular application is synthetic biology.

70. Several participants suggested the use of the existing frameworks for risk assessment of LMOs for assessing synthetic biology developments. A different participant indicated that sometimes existing risk assessment methodologies are not fit for purpose when it comes to synthetic biology, especially in dealing with components and products.

[17] Kosicki et al., 2018, Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements, *Nature Biotechnology*, 36(8), doi:10.1038/nbt.4192.

71. The intervention of a participant stated that if genetic resources and derivates are used to produce products through synthetic biology, the third objective of the Convention on Biological Diversity, in relation to the fair and equitable sharing of the benefits arising from the utilization of genetic resources could be impacted.

Topic 5: 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

72. The aim of discussions under this topic was to provide examples of synthetic biology organisms (if any) that may fall outside the definition of living modified organisms as per the Cartagena Protocol. Participants were reminded that the AHTEG in 2017 concluded that "most living organisms already developed or currently under research and development through techniques of synthetic biology, including organisms containing engineered gene drives, fell under the definition of LMOs as per the Cartagena Protocol" and were therefore requested to provide examples of possible changes to this situation (if any).

73. A number of interventions expressed the view that organisms produced thus far through synthetic biology fall under the definition of an LMO as per the Cartagena Protocol.

74. Two cases were pointed out as possibly falling outside of the definition of LMOs. The first case was organisms whose genomes had been edited without the use of nucleic acids using only protein reagents (Mega nucleases, ZFN, TALEN) introduced into the cell. The second case was related to virus-like macromolecular assemblies.

75. A participant pointed out that certain applications of xenobiology are synthetic biology, but not all are LMOs. The participant referred to chemically modified organisms[18] (CMO) that are modified with non-canonical nucleic acids or non-canonical amino acids (ncAAs), noting that both examples would fall under the operational definition of synthetic biology (as acknowledged in decision XIII/17), but CMOs that are modified with non-canonical amino acids would not fall under the definition of LMO since they do not represent a novel combination of genetic material.

76. A participant indicated that as per the Protocol's definition of an LMO, the use of in vitro nucleic acid techniques is not limited to only DNA as genetic material, mentioning that living organisms that are modified to contain genetic material other than DNA (such as XNA) for replication would fall under the definition of an LMO. Under the same intervention, the participant indicated that examples of LMOs that fall outside the definition of the Protocol apply to some living protocells that are still in an early state of research.

77. A participant provided information on possible cases where further analysis might be needed to decide if the organisms should be considered LMOs as defined in the Protocol. The examples provided where:

(a) The entity in question is a living organism that possesses a novel combination of genetic material but is not obtained using modern biotechnology;

(b) The entity in question is a living organism that possesses genetic material from the same species or sexually compatible species;

(c) The entity in question is a living organism that possesses a novel combination of genetic material obtained using modern biotechnology, but that genetic material has no similarity with any naturally occurring genetic material;

(d) The entity in question is a living organism that has been synthesized entirely in vitro;

[18] Acevedo-Rocha, C and Budisa, N, 2011, On the road towards chemically modified organisms endowed with a genetic firewall, Angewandte Chemie, 50, 31, https://doi.org/10.1002/anie.201103010

(e) The entity in question is a living organism that possesses a novel combination of genetic material, but only in cells and tissues that do not participate in sexual and non-sexual reproduction under natural conditions;

(f) The entity in question is not a living organism.

Topic 6: Sharing of experiences on detection, identification and monitoring of organisms, components and products of synthetic biology

78. Under this topic, participants were encouraged to share information related to experiences with the detection, identification and monitoring of organisms, components and products of synthetic biology, being as specific as possible and providing examples.

79. The moderator posed the following questions:

(a) Which tools are currently available for detecting, identifying and monitoring organisms, components and products of synthetic biology?

(b) Does the novelty that some organisms, components and products of synthetic biology might present require the development of additional detection, identification and monitoring tools, other than those that already exist?

(c) Could the current analytical techniques be used to distinguish between products of synthetic biology and their naturally occurring or chemically synthesized counterparts?

80. In general, participants noted that most of the techniques used for detection and identification of traditional LMOs were applicable for new, synthetically derived organisms. Polymerase chain reaction (PCR) was highlighted due to its common usage and its ability to detect insertions, deletions, unique and specific DNA sequences, and genomic variations. Some have pointed out that in cases where transgenes have been incorporated into the genome or RNA was used for the genetic material, standard PCR would also be enough for detection and identification. Some participants also suggested that hybridization assays, protein detection, and sequencing could also be utilized. In particular, an intervention supported protein methods as being more rapid and cost-effective in situations when release has occurred, or large monitoring is required. Another participant provided an example of antibody-based detection, which demonstrated higher detection rates than cDNA approaches for synthetic viruses.[19]

81. Some participants mentioned the importance of utilizing the mechanisms, methods, and certified references already established to give rapid, cost-effective results, promote collaborations, and support information sharing. Additionally, a participant added that analytical methods would need to be harmonized and validated, such that they could be implemented in a systematic way. One participant noted that identification methods should be developed not only for when a negative effect is known, but also for LMOs whose effects may not be entirely obvious.

82. Several participants noted that successful detection relies on knowing what should be detected, especially for PCR-based tools. Due to the event-specific nature of the changes, some participants suggested that cooperating with developers to disclose this information or to provide methodologies would facilitate detection and identification.

83. A few participants mentioned tracking the authorization of synthetic organisms and products using international databases.

84. Some interventions emphasized the importance of new unique identifiers to prevent errors in identification and avoid liability issues. Another intervention suggested sworn statements and traceability measures if tools cannot reliably detect differences in products.

[19] United States Environmental Protection Agency (2018), EPA Review of Product Characterization, Toxicity Waiver Requests, Allergenicity, and Human Health Data for Plant-Incorporated Protectants (PIPs): Defensin proteins derived from spinach (Spinach oleracea L.) Sod2, Sod2*, Sod7, Sod8, https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2018-0040-0007&contentType=pdf

85. Overall, gene editing received most of the attention. Some participants noted that gene editing did not constitute synthetic biology and would not require regulation or detection. Others believed there should be regulation, and, thus, detection and identification were important. Some participants acknowledged the difficult technical challenges presented by gene editing, noting that difficulties lie in distinguishing how the mutation arose, whether through editing, conventional mutagenesis, or a naturally occurring mutation.

86. In terms of differentiating between natural and synthetic products, some participants noted that current techniques should be sufficient by searching for minor contaminants or modifications created in either process.

87. A different intervention mentioned a new technique called "sensitive mutation detection using sequencing", which has been used to detect rare cancer mutations and could be successful at determining single nucleotide changes, while mitigating error in PCR and sequencing analysis.[20] However, when the event is unknown, a few participants noted the financial constraints of using high-throughput methods, such as sequencing.

88. When considering organisms containing non-natural amino acids and nucleotides, participants described current methods, such as chromography and mass-spectrometry, to detect both unnatural amino acids and nucleotides. Additionally, a participant mentioned that for xenonucleotide detection, PCR, hybridization probes, and sequencing could be adjusted to accommodate changes in chemistries. The participant also indicated that a greater challenge will arise when the site of the xenonucleotides is not known. For non-natural amino acids, either mass spectrometry or immunological detection methodologies were suggested.

89. A participant envisioned difficulty detecting differences in cases wherein processing removes DNA and protein from the product.

90. Overall, opinions were divided on the necessity of distinguishing between natural and synthetic products. Some participants indicated that there should not be a requirement to use analytical techniques to differentiate between the two unless there is a risk. In contrast, other participants stressed that distinguishing between natural and synthetic products should not be limited to a related risk. One intervention pointed towards labelling for consumers. One participant noted that products may have varying intellectual property rights, thus leading to differential socioeconomic benefits. Therefore, a need to distinguish the products exists.

Topic 7: Relationship between synthetic biology and the criteria set out in decision IX/29

91. The discussion under this topic focused on providing information 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 (new and emerging issues: synthetic biology).

92. Forum interventions contained general comments as well as specific statements in relation to the criteria for new and emerging issues.

(a) Relevance of the issue to the implementation of the objectives of the Convention and its existing programmes of work (decision IX/29, para. 12 (a))

93. It was pointed out that organisms, components and products of synthetic biology can have neutral, positive or negative effects on biodiversity. It was indicated that synthetic biology is relevant for the implementation of the objectives of the Convention and its existing programmes of work. Some participants indicated that, while synthetic biology can be said to be relevant to the implementation of the objectives of the Convention, living organisms produced through synthetic biology are LMOs covered by the Cartagena Protocol and, therefore, are not new and emerging.

[20] Boutigny, AL, Barranger, A., De Boisséson, C., Blanchard, Y., & Rolland, M., 2019, Targeted Next Generation Sequencing to study insert stability in genetically modified plants, *Scientific Reports*, 9(1):2308 doi: 10.1038/s41598-019-38701-9.

94. Paragraph 11 of decision 14/19, in which the Conference of the Parties called upon Parties and other Governments, taking into account the current uncertainties regarding engineered gene drives, to apply a precautionary approach, in accordance with the objectives of the Convention was also highlighted under this criterion. Another participant also referred to the need for a precautionary approach, in particular for ecosystems, protected areas and territories of indigenous peoples and local communities. The intervention highlighted the need to carefully analyse if a CRISPR-based gene drive could be a global conservation solution or a threat. On a similar note, the importance of the free prior and informed consent of indigenous peoples and local communities was also highlighted.

95. The relevance of synthetic biology in relation to the third objective of the Convention was also mentioned, indicating that synthetic biology increasingly detaches itself from genetic material and, thus, the control of providers. Others noted that an important aspect to be considered is the distribution of benefits arising from access to genetic resources and derivatives when components and products of synthetic biology are developed from the information found in bioinformatic media.

(b) New evidence of unexpected and significant impacts on biodiversity (decision IX/29, para. 12 (b))

96. On this criterion, some participants indicated that, thus far, there is no evidence for unexpected and significant impacts on biodiversity resulting from synthetic biology. Others were of the view that the current lack of evidence about negative impacts does not mean that such evidence does not exist.

97. Focusing on LMOs, one intervention indicated that the fact that no evidence of unexpected and significant impacts had been identified pointed to the fact that current regulatory mechanisms were providing the necessary tools to address potential impacts on biodiversity arising from the use of LMOs, which are equally applicable to LMOs that are derived from synthetic biology applications. On the other hand, it was stated that the fact that, thus far, synthetic biology organisms are LMOs, does not mean that their potential impacts are equal to that of organisms produced through classical genetic engineering, indicated that it would be like comparing the first machines with modern robots.

(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 (decision IX/29, para. 12 (c))

98. Some participants were of the view that there is no urgency to address the issue, while others held opposing views.

99. One participant stated that, since some of the synthetic biology developments may result in potential negative effects on biodiversity, the urgency of addressing this issue in the effective implementation of the Convention is considered to be high. Nonetheless, the same participant also indicated 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; mentioning that if this is taken into account, urgency would be higher for those organisms that do not fall under the definition of an LMO and that could pose a negative environmental effect. Others indicated that the rapid pace of development synthetic biology is not necessarily a cause for concern.

100. It was mentioned that the reports of previous AHTEG meetings recognized that rapid change is not unique and not inherent to this technology. One participant was of the view that synthetic biology is a very broad and highly dynamic field of research, noting that even if so far synthetic biology organisms result in LMOs, this may not be the case in the future, and it is difficult to predict when this may happen; therefore, suggesting that the issue should be addressed now.

101. It was also noted that the presumed efficiency of gene-drive modified organisms may lead to calls for their release in crisis situations before there is adequate knowledge of their ecological effects, and before mitigation plans for unintended harmful consequences are in place. The urgency to enhance capacities to assess and monitor the possible effects of synthetic biology on ecosystems was also pointed out.

(d) Actual geographic coverage and potential spread, including rate of spread, of the identified issue relating to the conservation and sustainable use of biodiversity (decision IX/29, para. 12 (d))

102. The intervention of some participants indicated that the actual geographic coverage and potential spread of synthetic biology organisms is so far equal to that of current LMOs. Others indicated that the geographic restriction of organisms containing engineered gene drives may potentially be more difficult compared to other LMOs.

103. The limited capacity of current modelling systems as a tool to capture the practical consequences (i.e. the variance of estimates can be too high to be useful) was also noted.

(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 (decision IX/29, para. 12 (e))

104. It was pointed out by some participants that since current and near-future organisms to be released into the environment obtained through synthetic biology are LMOs, their safety could be addressed under the Cartagena Protocol. It was also mentioned that in the future, fast replicating and fast-spreading LMOs (such as some insects) with engineered gene drives can be released and may have negative effects on biodiversity, indicating that tools to mitigate these effects are so far limited. On a similar note, it was pointed out that even if many of the current tools may be useful, they may not be sufficient for certain cases, and that this should be considered proactively and not reactively.

105. Another intervention noted that there was no evidence in the reports of the two previous AHTEGs of absence or limited availability of tools to limit or mitigate potential negative impacts of organisms that result from synthetic biology techniques.

(f) Magnitude of actual and potential impact of the identified issue on human well-being (decision IX/29, para. 12 (f))

106. For this criterion, interventions of some participants stated that the magnitude of these potential effects cannot be predicted in a generalized manner and must be assessed on a case-by-case basis.

(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 (decision IX/29, para. 12 (g))

107. It was mentioned that organisms, components and products of synthetic biology can have neutral, positive or negative effects on several productive sectors, such as agriculture, medicine, biofuel production and the food sector (e.g. additives, colorants, flavourings). Another participant indicated that economic impacts of synthetic biology cannot be addressed on a general basis, since they are dependent on the individual product. The intervention of a different participant mentioned that this is an area that needs more attention and engagement from indigenous peoples and local communities in developing countries who may depend on natural products, agriculture and conservation for their well-being.

(g) General comments on topic 7

108. The Forum participants also provided general comments regarding the relationship between synthetic biology and the criteria set out in decision IX/29.

109. The participants had different views on whether or not synthetic biology should be considered a new and emerging issue.

110. Participants' opinions also varied on how to interpret and apply the criteria for new and emerging issues. Some indicated difficulty in applying the criteria for new and emerging issues to the broad and diverse area of synthetic biology. Some suggested that it would be more practical to break the package into pieces (i.e. sub-areas such as xenobiology, minimal cells, gene drives) and test the criteria against these sub-areas.

111. Some participants were of the view that, since synthetic biology organisms fall thus far under the definition of an LMO, they should be covered by the Cartagena Protocol, and duplication between actions under the Convention and the Protocol should be avoided. Others commented that the Protocol may not cover all synthetic biology applications (i.e. components and products) and reiterated that it only applies to Parties to this treaty and not to all CBD Parties. One participant referred to Conference of the Parties decision 14/19, whereby Parties agreed that that broad and regular horizon scanning of the most recent technological developments is needed for reviewing new information regarding the potential positive and potential negative impacts of synthetic biology vis-à-vis the three objectives of the Convention and those of its Protocols, indicating that that provision points to the fact that it is not sufficient to treat synthetic biology only at the level of the Cartagena Protocol.

112. A participant indicated that Article 8(g) of the Convention goes beyond the scope of the Cartagena Protocol, indicating that a synthetic biology organism that is regarded as an LMO within the scope of the Cartagena Protocol is not excluded from the requirements of Article 8(g) of the Convention.

113. Some participants noted the importance of focusing the identification of new and emerging issues on not only "actual" but "potential" impacts, indicating that, if the focus is only on identifying new and emerging developments when negative impacts on the objective of the Convention are already measurable, the tool of "new and emerging issues" will fail because it only takes effect after something has happened. In this respect, a participant noted that, even if the criteria include consideration of both "potential" and "actual", a "robust analysis" requires that "potential" scenarios be informed by "actual" evidence.

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