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AD HOC TECHNICAL EXPERT GROUP ON RISK ASSESSMENT AND RISK MANAGEMENT UNDER THE CARTAGENA PROTOCOL ON BIOSAFETY
Mexico City, 25-29 July 2016

SUMMARY OF THE OUTPUTS OF THE ONLINE DISCUSSION ON "RISK ASSESSMENT OF LMOS PRODUCED THROUGH SYNTHETIC BIOLOGY" HELD UNDER THE OPEN-ENDED ONLINE FORUM

1. The document herein attached was prepared by the Secretariat taking into account views from the "Open-ended Online Forum" and members of the AHTEG, in response to decision BS-VII/12.

2. The present document is being presented for the consideration of the AHTEG at its face-to-face meeting from 25 to 29 July 2016 in Mexico City.

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OPTIONS REGARDING THE DEVELOPMENT OF GUIDANCE ON RISK ASSESSMENT OF LMOS DEVELOPED THROUGH SYNTHETIC BIOLOGY

At its face-to-face meeting held in November 2015 in Brasilia, Brazil, the AHTEG on Risk Assessment and Risk Management decided to recommend to the COP-MOP the development of additional guidance on "risk assessment of LMOs produced through synthetic biology". Furthermore, pending the outcomes of the twentieth meeting of SBSTTA that could impact the development of further guidance on the topic, the AHTEG also decided to prepare an outline on the topic for the COP-MOP in order to facilitate its consideration and further development of the topic as separate guidance.

The present document draws from a discussion on "possible considerations during the environmental risk assessment of LMOs developed or created through approaches commonly referred to as 'synthetic biology'" that was held from 13 to 27 June 2016 under the Online Forum on Risk Assessment and Risk Management with the objective of providing input to the AHTEG.1

In the discussion, experts from 6 Parties (Belarus, China, Finland, Malaysia, Mauritania and Slovenia) supported the AHTEG in recommending to the COP-MOP the development of guidance on risk assessment of LMOs developed through synthetic biology, whereas experts from 5 Parties (Italy, Japan, Netherlands, New Zealand and United Kingdom) did not support such recommendation. Moreover, experts from 4 Parties (Brazil, Germany, Kenya and Mexico) were either neutral or had diverging views within each Party. In terms of the total number of experts representing Parties which participated in the discussion, the majority (15 out of 27) did not support the development of guidance on risk assessment of LMOs produced through synthetic biology.

In reflecting the views from Parties and as a way forward, the following two options for a recommendation to the COP-MOP have been identified:

- **Option 1:** Specific guidance on risk assessment of LMOs developed through synthetic biology is needed;

- **Option 2:** Specific guidance on risk assessment of LMOs developed through synthetic biology is currently not needed.

The following section summarizes views that were shared in response to specific considerations that were brought forward during the online discussion. For ease of understanding, supporting arguments were grouped according to the two options above.

1 The discussion is available at http://bch.cbd.int/onlineconferences/onlineconferences/forum_ra/discussion.shtml.

SPECIFIC CONSIDERATIONS AND SUPPORTING ARGUMENTS UNDER EACH OPTION

Comparative approach **–** Synthetic biology may lead to the development or creation of LMOs containing new features that are significantly different from those in the original organism or from organisms existing in nature.

Supporting arguments for "Option 1":

Although the boundary between synthetic biology and modern biotechnology is not well-defined, techniques that are used to produce LMOs and are commonly referred to as synthetic biology include, but are not limit to, genome editing, gene drive, and metabolic pathway engineering.

The comparative approach to risk assessment is an example of where the use of synthetic biology techniques may create qualitatively special challenges for risk assessment because the standard approach to risk assessment is comparative. The comparative approach may not be suitable or enough for the risk assessment of LMOs developed through synthetic biology due to their depth or kind of intervention making the resulting LMOs significantly different to existing organisms.

Particular attention needs also to be given to *de novo* genes and *de novo* metabolic pathways, or where new traits may be introduced into the environment, either intentionally or unintentionally.

The lack of suitable comparators will present a challenge in risk assessments based on a comparative approach. This requires particular and special consideration by risk assessors, and is one of the most important reasons as to why additional guidance on synthetic biology is needed.

Supporting arguments for "Option 2":

Challenges in the comparative approach to risk assessment is not an issue that is specific to synthetic biology, and examples of solutions that have been utilized by regulators as required on a case-by-case basis can be provided (e.g. LMOs with modifications that cannot be compared to the near isogenic non-LMO under the same conditions, such as LM drought tolerant crops).

It is noted that other organizations have successfully addressed these challenges. For example, the US National Institutes of Health recently updated its biosafety guidelines for US scientists working with LMOs modified using the methods of synthetic biology ("NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules"). The examples of LMOs that have been extensively modified which were raised during the online discussion were safely reviewed under these guidelines.

Moreover, it is noted that the existing "Guidance on Risk Assessment of LMOs" contains a section addressing comparators ("The Choice of Comparators"), and the AHTEG may be advised to review that section for broader applicability to organisms other than LM plants. New guidance should only be developed if and when concrete examples and experience from risk assessors so require.

LMOs being developed faster and with an increased number of modified traits – Synthetic biology aims at increasing the precision and the predictability of the changes in the resulting organisms. Synthetic biology will also lead to a faster development of LMOs through the use of automation and to more numerous and complex changes and novel traits.

Supporting arguments for "Option 1":

The possibility that unintended and unexpected adverse effects emerging as a result of an interaction between the changes as well as interactions between the changes and the environment cannot be ruled out and will make the evaluation of the overall risk of such LMOs more complex.

The speed of new developments is going to increase leading to challenges in the existing administrative structures and resources dealing with risk assessment of LMOs. How to respond to these challenges and the means to adapt guidance and develop capacity should be discussed.

Supporting arguments for "Option 2":

While the number and complexity of modifications might make the risk assessment of LMOs developed through synthetic biology more challenging than for simpler LMOs, it is the nature and experience with the type of modification that are most relevant. For example, an LMO with several well-understood and harmless novel traits will be easier to assess than an LMO with a single, less understand and potentially harmful novel trait.

In the future, methodologies may need to be updated and adapted for current and future developments and applications of synthetic biology based on an established process to monitor and assess the state of knowledge within the field of synthetic biology on a regular basis.

Potential to alter entire wild populations, whole species as well as ecosystems – Synthetic biology techniques can use mechanisms called "gene drives" to modify traits that are intended to be passed on to entire wild populations, instead of only to some members of the population. Gene drive systems may be able to address serious threats to health and ecosystems by, for example, eliminating diseases and eradicating invasive alien species, but gene drives also have the potential to cause irreversible adverse effects on beneficial organisms and ecosystems.

Supporting arguments for "Option 1":

Automation of synthetic biology techniques will make it easier to develop LMOs containing gene drive systems, and robust methods are called for in order to assess the risks of gene drives being transferred to other members of the same species in a non-contiguous geographical zone and to non-target species. These methods must rely, among other things, on in-depth knowledge of the ecology of target and non-target species.

It is noted that gene flow per se may not be a qualitatively unique issue for LMO risk assessment, but in the case of gene drive systems both the 'drive' as a trait, and the effect of the gene must be investigated.

The uniqueness of gene drive systems, their intended purpose to alter wild populations and ecosystems, and the predicted increase in the number of LMOs developed through synthetic biology that will carry gene drive systems justify particular guidance on risk assessment of LMOs developed through synthetic biology.

Supporting arguments for "Option 2":

Techniques that use gene drive systems are not necessarily limited to synthetic biology. The existing "Guidance on Risk Assessment of LMOs", and specifically the section on "Risk Assessment of Living Modified Mosquitoes", already includes discussions of LMOs carrying gene drive systems and with potential to alter wild populations. Guidance focusing on specific types of LMOs and traits are far more useful than guidance about a specific technology type.

The experience of risk assessors, as much as the contribution of specialists like entomologists, will be a valuable tool to show in which extent the current legal framework for environmental risk assessment can be used to assess LMOs with potential to alter entire wild populations and if any adaptation in this framework is need based on concrete cases.

Furthermore, in line with paragraph 66(e) of the report of the AHTEG on Synthetic Biology, coordination and establishment of synergies with other UN and international organizations such as the World Health Organization (WHO) will be useful in assessing the risks of this type of LMOs.

Increased accessibility to techniques of synthetic biology – Synthetic biology approaches will become more accessible and easy to use by the general public through "do-it-yourself" projects.

Supporting arguments for "Option 1":

The increased number of LMOs developed outside of formally established laboratory facilities may change the way in which risk assessment and risk management methodologies are used to assess, avoid or minimize the potential adverse impacts of such LMOs.

Supporting arguments for "Option 2":

Increased accessibility to synthetic biology techniques will not change the way in which risk assessment and risk management methodologies are used. Moreover, this is not a specific issue for synthetic biology but rather a matter of strengthening national legislation and compliance with risk assessment regulations. National regulations may need to be reviewed and/or implemented based on an established process to monitor and assess the state of knowledge within the field of synthetic biology on a regular basis.

One practical way forward is to devote greater effort in making the existing "Guidance on Risk Assessment of LMOs" more widely available to the citizen scientists working with LMOs.

Detection of LMOs developed through genome editing – Methods to detect and identify LMOs, and their specificity, sensitivity and reliability are a point to consider in Annex III of the Protocol. Genome editing may create small changes at the DNA level (e.g. single nucleotide changes) both in target as well as off-target sites across the genome, and the resulting LMOs will not be easily characterized through methods that are currently in use.

Supporting arguments for "Option 1":

It will be difficult to assess the rate of outcrossing of LMOs containing small off-target changes at the DNA level during pre-market risk assessments and to detect such LMOs during post-market risk management and monitoring. Consequently, it may be difficult to establish routes of exposure and possible causal links between an LMO and an adverse effect or to a change that could lead to an adverse effect.

Supporting arguments for "Option 2":

Issues related to challenges in the detection and characterization of LMOs are not specific to synthetic biology. The technical aspects regarding detection and identification of LMO, including capacity building activities, are being dealt with in another forum. The existing "Guidance on Risk Assessment of LMOs" should stay current on the types of molecular characterization for risk assessors to request from product developers.

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