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From

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To

Secretariat of the Convention on Biological Diversity

Dear Sir/Madam:

Pursuant to request Ref.: SCBD/CP/DC/MA/MW/87791, dated 14 December 2018, to submit to the Secretariat (secretariat@cbd.int) information and supporting documentation on the four topics referred to [below] as soon as possible, but no later than 15 February 2019. The following document and supporting information are provided in order to be made available for consideration by the online forum and the Ad Hoc Technical Expert Group (AHTEG) on synthetic biology.

The information provided in this submission primarily concerns the misperception implied in Decision CBD/COP/DEC/14/19, paragraph 9, that all engineered gene drives are synthetic biology, and therefore a new and emerging issue. In earlier discussions on synthetic biology, it was clear that only some LMOs containing gene drives might be considered synthetic biology. In its decision at COP13, the COP agreed that synthetic biology "*can also apply to some living modified organisms containing gene drives[.]*" (Decision CBD/COP/DEC/XIII/17, paragraph 2). Some of these same observations were captured in the peer reviews of the 2017 report of the AHTEG on synthetic biology (CBD/SYNBIO/AHTEG/2017/1/3; See the peer reviews of this report from the Netherlands, Australia, and PRRI). That AHTEG report, which implies that all gene drives are synthetic biology, formed the basis of the recommendations from SBSTTA22 and eventually the Decision on synthetic biology at COP14. In its future discussions, the AHTEG should carefully consider whether it is appropriate to include all gene drives, and particularly LMOs containing gene drives, as part of synthetic biology. The information in this submission will be useful in the AHTEG's deliberations on this point.

We agree with Decision CBD/COP/DEC/XIII/17, paragraph 2, that the term "synthetic biology" can apply to [only] some LMOs containing gene drives, and this must be determined on a case-by-case basis. We believe that none of the current examples of gene drives in LMOs fit into the "synthetic biology" class of organisms. Most examples of engineered (or 'synthetic'[1]) gene drives currently contained in LMOs have been developed using tools of modern biotechnology, as defined in the Cartagena Protocol. These LMOs are captured under the Cartagena Protocol, and the risks can be assessed using the same approach to risk assessment as other LMOs that are the subject of the Protocol. Therefore, these LMOs containing gene drives may not meet the operational definition of synthetic biology that the AHTEG is currently considering in their deliberations.

The operational definition of synthetic biology established by the Convention on Biological Diversity was adopted by the AHTEG on synthetic biology in order to facilitate discussion of the topic:

> *"…synthetic biology is a further development and new dimension of* ***modern biotechnology*** *that combines science, technology and engineering to facilitate and accelerate the understanding, design, redesign, manufacture and/or modification of genetic materials, living organisms and biological systems" (emphasis added).*

The AHTEG recognized that synthetic biology is an **extension** of modern biotechnology, although what constitutes a 'further development and new dimension' is still unclear. Living modified organisms (LMOs), **including those containing gene drives,** that have been obtained through the use of modern biotechnology, not through methods that are further developments and are a new dimension of that field, are not new and are already the subject of the Cartagena Protocol on Biosafety:

> *"Living modified organism" means any living organism that possesses a novel combination of genetic material obtained through the use of* ***modern biotechnology****;(Secretariat of the Convention on Biological Diversity, 2000)(emphasis added).*

Modern biotechnology is defined in the Protocol as:

'*The application of:*

a. In vitro nucleic acid techniques, including recombinant DNA and direct injection of nucleic acid into cells or organelles, or

b. Fusion of cells beyond the taxonomic family,

that overcome natural physiological reproductive or recombinant barriers and that are not techniques used in traditional breeding and selection.'

[1] One source of confusion comes from the use of the term 'synthetic gene drives', which we assert is the same as 'engineered gene drives', i.e. gene drives obtained through the use of modern biotechnology, and not synthetic biology.

If the operational definition continues to be the basis of the discussion of synthetic biology, the AHTEG should consider whether any LMOs that have been obtained using modern biotechnology, including LMOs that contain engineered gene drives, should be considered synthetic biology, and whether the criteria set out in Decision IX/29, paragraph 12 to identify a new and emerging issue have been met in these cases. It is possible that there are activities and products of synthetic biology that cannot be classified as LMOs, or that have been obtained using techniques that do not fit the definition of modern biotechnology, and these, after consideration of the criteria set out in Decision IX/29, paragraph 12, might merit status as a new and emerging issue. These could then be the subject for further deliberations by the AHTEG. While there might be gene drive systems that are not LMOs obtained through modern biotechnology that could be considered synthetic biology and therefore may be a new and emerging issue, we are unaware of any such examples.

A determination regarding these non-LMO, post-modern biotechnology aspects of synthetic biology, compared to LMOs obtained through modern biotechnology, is not possible until there is agreement on a formal rather than operational definition. Once this definition is established, then, according to decision XII/24, paragraph 2, there must be a robust analysis using the criteria set out in paragraph 12 of Decision IX/29.

Herein, we provide information and references under point (a) of the request for information, to encourage a discussion and inform the deliberation regarding gene drives as synthetic biology by the online forum and AHTEG. The information we provide supports the following points:

1) Gene drives occur in nature

2) Current techniques used to obtain LMOs containing gene drives fit the definition of modern biotechnology under the Cartagena Protocol.

3) Existing approaches to risk assessment of LMOs can be used for LMOs containing engineered gene drives released into the environment.

4) There is overlap in global policy discussions on synthetic biology, gene drives, and genome-editing to be sorted out.

(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;

The information provided below is relevant to a determination that gene drives, whether or not they meet the definition of synthetic biology, do not meet the criteria for a new and emerging issue related to the conservation and sustainable use of biodiversity.

1) Gene drives occur in nature and are not something completely novel.

The concept of using synthetic gene drives to change the genetic composition of wild populations is derived from the observation of their occurrence in nature. Examples of documented naturally occurring gene drives are described in the following references:

- Burt, A., and Crisanti, A. (2018). Gene Drive: Evolved and Synthetic. ACS Chemical Biology *13*.

- Burt, A., and Trivers, R. (2006). Genes in Conflict: the Biology of Selfish Genetic Elements (Belknap Press of Harvard University Press).

- Conner, A.J., Jacobs, J.M.E. 2019. A natural, conditional gene drive in plants. bioRxiv preprint, online Jan. 17, 2019. http://dx.doi.org/10.1101/519884doi:
- Lindholm, A.K., Dyer, K.A., Firman, R.C., Lila Fishman, Wolfgang Forstmeier, Luke Holman, Hanna Johannesson, Ulrich Knief, Hanna Kokko, Amanda M. Larracuente, et al. (2016). The Ecology and Evolutionary Dynamics of Meiotic Drive. Trends in Ecology & Evolution *31*, 315–326.

- National Academies of Sciences, Engineering, and Medicine (2016). Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values (Washington, D.C.: National Academies Press).

- Sandler, L., Hiraizumi, Y., and Sandler, I. (1959). Meiotic Drive in Natural Populations of Drosophila Melanogaster. I. the Cytogenetic Basis of Segregation-Distortion. Genetics *44*, 233–50.

- Werren, J.H., Nur, U., and Wu, C. I. (1988). Selfish genetic elements. Trends in Ecology & Evolution *3*, 297–302.

2) Current techniques used to obtain LMOs containing gene drives fit the definition of 'modern biotechnology' as defined for the Cartagena Protocol, and do not use 'further developments or new dimensions' of modern biotechnology.

These publications describe examples of gene drives in insects and rodents obtained by the techniques of modern biotechnology as defined in the Cartagena Protocol on Biosafety (Secretariat of the Convention on Biological Diversity, 2000), in particular the application of '*In vitro nucleic acid techniques, including recombinant DNA and direct injection of nucleic acid into cells or organelles'[.]*

- Buchman, A., Marshall, J.M., Ostrovski, D., Yang, T., and Akbari, O.S. (2018). Synthetically engineered Medea gene drive system in the worldwide crop pest Drosophila suzukii. Proceedings of the National Academy of Sciences of the United States of America *115*, 4725–4730.

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- Gantz, V.M., Jasinskiene, N., Taratenkova, O., Fazekas, A., Macias, V.M., Bier, E., and James, A.A. (2015). Highly efficient Cas9-mediated gene drive for population

modification of the malaria vector mosquito Anopheles stephensi. Proc. Natl. Acad. Sci. USA *215*, E6736–E6743.

- Hammond, A., Galizi, R., Kyrou, K., Simoni, A., Siniscalchi, C., Katsanos, D., Gribble, M., Baker, D., Marois, E., Russell, S., et al. (2016). A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector Anopheles gambiae. Nature Biotechnology *34*, 78–83.

- Kyrou, K., Hammond, A.M., Galizi, R., Kranjc, N., Burt, A., Beaghton, A.K., Nolan, T., and Crisanti, A. (2018). A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged Anopheles gambiae mosquitoes. Nature Biotechnology *36*, 1062–1066.

- Oberhofer, G., Ivy, T., and Hay, B.A. (2018). Behavior of homing endonuclease gene drives targeting genes required for viability or female fertility with multiplexed guide RNAs. *115*.

- Yosef, I., Edry-Botzer, L., Globus, R., Shlomovitz, I., Munitz, A., Gerlic, M., and Qimron, U. (2019). A genetic system for biasing the sex ratio in mice. BioRxiv 515064.

3) There is a growing body of literature that illustrates the use, or analyzes the adequacy of, existing approaches to risk assessment for environmental release of LMOs containing other engineered 'traits' (e.g., GM crops, GM insects) to LMOs containing engineered gene drives.

- Beech, C.J., Vasan, S.S., Quinlan, M.M., Capurro, M.L., Alphey, L., Bayard, V., Bouaré, M., McLeod, M.C., Kittayapong, P., Lavery, J.V., et al. (2009). Deployment of Innovative Genetic Vector Control Strategies: Progress on Regulatory and Biosafety Aspects, Capacity Building and Development of Best-Practice Guidance. *17*, 11.

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- National Academies of Sciences, Engineering, and Medicine (2016). Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values (Washington, D.C.: National Academies Press).

- Okumu, F., de Andrade, P.P., Savadogo, M., James, S., Roberts, A., Quemada, H., and Singh, J.A. (2017). Results from the Workshop "Problem Formulation for the Use of Gene Drive in Mosquitoes." The American Journal of Tropical Medicine and Hygiene *96*, 530–533

- Westra, J., van der Vlugt, C.J.B., Roesink, C.H., Hogervorst, P.A.M., and Glandorf, D.C.M. (2016). Gene Drives Policy Report (National Institute for Public Health and the Environment (RIVM), Netherlands).[2]

4) There are currently overlapping policy-related discussions on synthetic biology, gene drives, and genome-editing taking place globally. The available information on these policy-related discussions on these issues, particularly in relation to the inclusion of gene drives as synthetic biology or not, are relevant to the discussions that will take place in the planned online forum and by the AHTEG. Here we list some information relevant to the policy discussions on these issues.

Synthetic biology policy

- Bailey, C., Metcalf, H., Crook, B. 2012. Synthetic biology. A review of the technology, and current and future needs from the regulatory framework in Great Britain. Research Report RR944. Health and Safety Laboratory for the Health and Safety Executive, UK.

- Carter, S.R., Rodomeyer, M., Garfinkel, M.S., Friedman, R.M. 2014, May. Synthetic Biology And the US Biotechnology Regulatory System: Challenges and Options. J. Craig Venter Institute.

- European Academies Science Advisory Council (EASAC) 2010, December. Policy Report 13. Realising European potential in synthetic biology: scientific opportunities and good governance. ISBN: 978-3-8047-2866-0. This report can be found at www.easac.eu

- Gray, P., Meek, S., Griffiths, P., Trapani, J., Small, I., Vickers, C., Waldby, C., and Wood, R. (2018). Synthetic Biology in Australia: An Outlook to 2030. Report for the Australian Council of Learned Academies, www.acola.org.au.

- OECD (2014), Emerging Policy Issues in Synthetic Biology, OECD Publishing. http://dx.doi.org/10.1787/9789264208421-en

- Presidential Commission for the Study of Bioethical Issues (PBSCI). 2010, December. New Directions. The Ethics of Synthetic Biology and Emerging Technologies. Washinton DC, USA. www.bioethics.gov.

- Science for Environment Policy (2016) *Synthetic biology and bidiversity.* Future Brief 15. Produced for the European Commission DG Environment by the Science Communication Unit, UWE, Bristol. Available at: http://ec.europa.eu/science-environment-policy

[2] It should be noted that while Westra et al. (2016) did not find existing risk assessment methodology suitable for contained use risk assessment, they concluded that existing risk assessment approaches for environmental release were suitable.

Genome-editing policy

- Council for Agricultural Science and Technology (CAST). 2018. *Genome Editing in Agriculture: Methods, Applications, and Governance—A paper in the series on The Need for Agricultural Innovation to Sustainably Feed the World by 2050*. Issue Paper 60. CAST, Ames, Iowa.

- Dronov, R. and Howard, W. 2014. Gene Editing and CRISPR. Occasional Paper Series Issue 14, September 2014. Office of the Chief Scientist, Australian Government Chief Scientist.

- Duensing, N., Sprink, T., Parrott, W.A., Fedorova, M., Lema, M.A., Wolt, J.D., and Bartsch, D. (2018). Novel Features and Considerations for ERA and Regulation of Crops Produced by Genome Editing. Frontiers in Bioengineering and Bio technology *6*, 79.

- Royal Netherlands Academy of Arts and Sciences (November 2016). *Genome Editing, Position Paper of the Royal Netherlands Academy of Arts and Sciences.* Amsterdam, KNAW.

- Shukla-Jones, A., Friedrichs, S., and Winickoff, D. (2018). Gene editing in an international context: Scientific, economic and social issues across sectors.

- Whelan, A.I. and Lema. M.A. 2015. Regulatory framework for gene editing and other new breeding techniques (NBTs) in Argentina. GM Crops Food. 6(4):253-265. doi: 10.1080/21645698.2015.1114698

- Wolt, J.D., Wang, K., and Yang, B. (2016). The Regulatory Status of Genome-edited Crops. Plant Biotechnology Journal *14*, 510–518.

Gene drive policy

- Australian Academy of Science. 2017, May. Discussion Paper. Synthetic Gene Drives in Australia: Implications of Emerging Technologies. www.science.org.au/gene-drives.

- Brossard, D., Belluck, P., Gould, F., and Wirz, C.D. (2019). Promises and perils of gene drives: Navigating the communication of complex, post-normal science. PNAS 201805874.

- Emerson, C., James, S., Littler, K., and Randazzo, F. (Fil) (2017). Principles for gene drive research. Science *358*, 1135 LP – 1136.

- Esvelt, K.M., Smidler, A.L., Catteruccia, F., and Church, G.M. (2014). Concerning RNA-guided gene drives for the alteration of wild populations. ELife *3*, 1–21.

- James, S., Collins, F.H., Welkhoff, P.A., Emerson, C., Godfray, H.C.J., Gottlieb, M., Greenwood, B., Lindsay, S.W., Mbogo, C.M., Okumu, F.O., et al. (2018). Pathway to Deployment of Gene Drive Mosquitoes as a Potential Biocontrol Tool for Elimination of Malaria in Sub-Saharan Africa: Recommendations of a Scientific Working Group. The American Journal of Tropical Medicine and Hygiene *98*, 1–49.

- National Academies of Sciences, Engineering, and Medicine (2016). Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values (Washington, D.C.: National Academies Press).

- Norwegian Biotechnology Advisory Board (2017). Statement on gene drives (Norwegian Biotechnology Advisory Board).

- Oye, K. (2014). Proceed With Caution. MIT Technology Review *117*, 11.

- Oye, K.A., Esvelt, K., Appleton, E., Catteruccia, F., Church, G., Lightfoot, K.S.B., Mcnamara, J., Smidler, A., and Collins, J.P. (2014). Regulating Gene Drives. Science *345*, 626–628.

- Rudenko, L., Palmer, M.J., and Oye, K. (2018). Considerations for the governance of gene drive organisms. Pathogens and Global Health.

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

Here we share examples from the literature that discuss or address potential positive and negative environmental impacts of some gene drives, whether or not they are considered synthetic biology.

- Collins, C.M., Bonds, J.A.S., Quinlan, M.M., and Mumford, J.D. (2019). Effects of the removal or reduction in density of the malaria mosquito, *Anopheles gambiae s.l* ., on interacting predators and competitors in local ecosystems: Malaria mosquito effects on ecosystems. Medical and Veterinary Entomology *33*, 1–15.[3]

[3] This publication addresses the impact of removal or suppression of populations of *Anopheles gambiae* on local ecosystems. Population suppression is the goal of some projects working with gene drives.

- HCB Scientific Committee (2017). Scientific Opinion in response to the referral of 12 October 2015 concerning use of genetically modified mosquitoes for vector control (Haut Conseil des Biotechnologies (France)).

- Lindholm, A.K., Dyer, K.A., Firman, R.C., Lila Fishman, Wolfgang Forstmeier, Luke Holman, Hanna Johannesson, Ulrich Knief, Hanna Kokko, Amanda M. Larracuente, et al. (2016). The Ecology and Evolutionary Dynamics of Meiotic Drive. Trends in Ecology & Evolution *31*, 315–326.[4]

- Min, J., Smidler, A.L., Najjar, D., and Esvelt, K.M. (2018). Harnessing gene drive. Journal of Responsible Innovation *5*.

- Okumu, F., de Andrade, P.P., Savadogo, M., James, S., Roberts, A., Quemada, H., and Singh, J.A. (2017). Results from the Workshop "Problem Formulation for the Use of Gene Drive in Mosquitoes." The American Journal of Tropical Medicine and Hygiene *96*, 530–533.

- Westra, J., van der Vlugt, C.J.B., Roesink, C.H., Hogervorst, P.A.M., and Glandorf, D.C.M. (2016). Gene Drives Policy Report (National Institute for Public Health and the Environment (RIVM), Netherlands).

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

We do not know of any new or old developments in gene drives, whether or not they are synthetic biology, that may fall outside the definition of living modified organisms.
See point (a)2 above.

[4] Discusses synthetic gene drives in light of what is observed with natural gene drives.

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Australian Academy of Science. 2017, May. Discussion Paper. Synthetic Gene Drives in Australia: Implications of Emerging Technologies. www.science.org.au/gene-drives.

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