OUTREACH NETWORK FOR
GENE DRIVE RESEARCH

Submission of information on synthetic biology in relation to decision 14/19

The Outreach Network for Gene Drive Research's purpose is to raise awareness of the value of gene drive research for the public good and the need for continuous efforts in its advancement. The Network's members are researchers and organizations working on gene drive research for the public interest, organizations involved in outreach, stakeholder engagement and other relevant fields, as well as funders or supporters of these activities. All Members commit to the Network's statement of mission and principles which includes the commitments to the intrinsic value of research, support of responsible research towards the public interest and engage in a transparent and evidence-based dialogue with stakeholders.

The Network is pleased to provide the Executive Secretary with relevant information to contribute to the work of the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology, as invited by the Conference of Parties in Decision 14/19.

The Network recommends that the the discussions on issues related to gene drive and synthetic biology take into account exisiting studies, guidelines and policies elaborated by other international organisations and scientific academies in order to avoid a duplication of the efforts. The discussion should be consistent with the key principle of the case by case assessment of risks and benefits of each single application and draw on the expertise of the AHTEG.

The following paragraphs provide information concerning the specific issue of gene drives under the four areas[1] identified by Decision 14/19.

1- The relationship between synthetic biology and the criteria set out in decision IX/29, paragraph 12.

The decision IX/29 sets out seven criteria for identifying new and emerging issues related to the conservation and sustainable use of biodiversity that should be addressed under the Convention. These criteria include elements such as the relevance of the issue for the objective of the

[1] The four areas identified by decision 14/19 are:

- 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;
- New technological developments in synthetic biology since the last meeting of the Ad Hoc Technical Expert Group in December 2017, including the consideration, among other things, of concrete applications of genome editing if they relate to synthetic biology, in order to support a broad and regular horizon scanning process;
- 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
- 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.

Convention, evidence and magnitude of its adverse impact on biodiversity and human well-being, the imminence of the risks caused by the issue and its potential spread, absence or limited availability of tools to limit its negative impacts.[2]

Concerning the relevance of synthetic biology to the implementation of the objectives of the Convention and its existing programmes of work, the Network supports the conclusion of the AHTEG on synthetic biology that most living organisms already developed or currently under research and development through techniques of synthetic biology, **including organisms containing engineered gene drives, fall under the definition of LMOs** as per the Cartagena Protocol[3].

Concerning the remaining six criteria of the decision IX/29 it is worth noting that an engineered gene drive is an approach being considered for a variety of possible applications. The risks and benefits associated with each gene drive application will vary, depending on the type of modification made, the species it is applied to, and the ecosystem and geography where the organism with the drive system would be used. Therefore, **any assessment of gene drive applications should be carried out on a case-by-case basis and** broad evaluations against the suggested criteria (impact on biodiversity, geographical spread, mitigation options…) are not possible. For example, the likelihood for a gene drive construct to pass into a closely related species (i.e. hybridization) will depend upon the particulars of the situation (e.g. whether there are any closely related species with which the target species can hybridize). Whether that construct passing to a closely related species would be considered a harm or a benefit will also depend on the required protection goal in the local situation (e.g., in the case of trait for malaria control if both are malaria vectors, then it may be considered a benefit). Similarly, there are many different types of engineered gene drive being investigated, some of which may persist indefinitely in a population, and others of which would disappear, and some of which would spread away from the point of release and others of which would not, and this diversity means it is not possible to make blanket statements about the risks associated with gene drive – case-by-case assessment is essential.

As for the specific criteria of the imminence of the risk (and benefits) potentially associated to gene drive, it is worth noting that current research indicates that it will take some years before any gene drive technology could be considered for field evaluation and several more before any potential use of gene drive applications for public health or conservation.

2- The current state of knowledge/environmental impacts:

Gene drive is a well-established field of research. First observed in the 1920s in mice and Drosophila, gene drive is a naturally occurring phenomenon that has been the subject of

[2] The full description of the criteria as set out in the decision is 1) Relevance of the issue to the implementation of the objectives of the Convention and its existing programmes of work;
(2 New evidence of unexpected and significant impacts on biodiversity; 3) 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; 4) Actual geographic coverage and potential spread, including rate of spread, of the identified issue relating to the conservation and sustainable use of biodiversity; 5) 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; 6) Magnitude of actual and potential impact of the identified issue on human well-being; 7)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

[3] Paragraph 28 AHTEG report of the meeting of the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology held from 5 to 8 December 2017, in Montreal, Canada; available at https://www.cbd.int/meetings/SYNBIOAHTEG-2017-01.

investigation for many years. Researchers have been studying if it is possible and appropriate to harness gene drives to address some of society's most intractable problems. Public health and biodiversity and ecosystem conservation are two of the main areas where this research has focused.

In the field of public health, several proposals have been made which would use gene drive to limit the spread of diseases, particularly those spread by insect vectors such as malaria. This could be done by spreading a trait which makes the vector organism unable to transmit the pathogen or one which affects the local population dynamics of the vector organism.

Additionally, gene drives approaches are currently being explored for conservation. Potential applications of gene drive in this field could enable the elimination of introduced, damaging invasive species which threaten native ecosystems or that carry infectious diseases that put the survival of other species at risk.

Current research in this field aims at using a gene drive approach in mice to facilitate a bias of subsequent rodent generations to all be single sex. The expected result is the creation of a final generation of mice unable to reproduce.

Besides the main research in public health and conservation, there is some early investigation of possible gene drive application in agriculture for controlling the population of agricultural pests, but there has been no successful development of any gene drive organisms with agricultural applications to date.

In all these fields, research is still exploring the potential benefits and risks of gene drive applications, including potential impacts on the ecosystem in which the applications would be deployed. Any assessment of these benefits and risks requires a case-by-case evaluation of each application by the competent national authorities.

Like in many other areas of research, many uncertainties must be addressed before any decision on use can be made. The assessment of risks by regulators and the decision of communities and policymakers whether possible applications of gene drive technology are desirable in light of their risks and benefits, depends on the information and outcomes provided by scientific research, including potential field trials and evaluations after laboratory development phases are complete. Key institutions, such as the African Union, the Royal Society and national academy of sciences, have called for continued work in this field, emphasizing the value of the opportunity and the need for informed case-by-case assessment of this technology by national authorities[4].

Scientists, alongside regulatory experts, funders and sponsors of the research on gene drive, are working together to ensure research is carried out safely and responsibly, by building on previous

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[4] African Union (2018), "**Report of the High-Level African Union Panel on Emerging Technologies (APET) on Gene Drives for Malaria Control and Elimination in Africa"** https://www.nepad.org/publication/gene-drives-malaria-control-and-elimination-africa.
Australian Academy of Sciences 2017 "**Synthetic gene drives In Australia: implications of emerging technologies**" https://www.science.org.au/files/userfiles/support/documents/gene-drives-discussion-paper-june2017.pdf
Royal Society 2018 **"Gene drive research why it matters" https://royalsociety.org/topics-policy/publications/2018/gene-drive-statement/**
National Academies of Science, Engineering, and Medicine (USA) (2016)"**Gene drives on the horizon: Advancing Science, Navigating Uncertainty and Aligning Research with Public Values**" https://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and

experiences, using published policy and information, and putting in place monitoring and containment systems to prevent accidental releases[5]. Research in the laboratory can rely on well-known protocols and procedures such as the ones used for LMOs and biocontrol agents, along with staff training. Laboratory containment measures are well documented in the literature, and have recently been complemented by additional considerations for gene drive (see for example Akbaria et al, 2015[6]). Progression in the evaluation of a gene drive product should be phased, based on the outcome of previous research phases on the safety and efficacy of the specific gene drive modified organism under study.

There are already several existing frameworks that offer guidance and describe best practices to ensure safe and responsible research on gene drive. The World Health Organisation recommended a phased testing pathway for genetically modified mosquitoes which is relevant to gene drive technologies[7]. In its 2016 report, the National Academy of Sciences, Medicine and Engineering (NASEM) also recommends a phased testing pathway combined with ecological risk assessments and proactive community engagement[8]. This was further expanded recently in a paper published by a scientific working group in 2018 (James et al, 2018). The group looked specifically at the development of gene drive mosquitoes for malaria control, but the pathway proposed outlines the same questions that would need to be considered for other applications of gene drive[9] [10].

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[5] For example, sponsors and supporters of gene drive research collaborated to publish a set of guiding principles for gene drive research. The developers and signatories of these principles are committed to mobilizing and facilitating progress in gene drive research by supporting efforts of the highest scientific and ethical quality, inspiring a transparent approach and backing biosafety measures. See Emerson et al., (2017) "**Principles of Gene Drive Research**" *Science* 01 Dec 2017:
Vol. 358, Issue 6367, pp. 1135-1136 http://science.sciencemag.org/content/358/6367/1135.full
Researchers working on gene drive have also been considering the safeguards needed to ensure safe laboratory and field practices. This is detailed in several publications, notably Akbary et al (2016) on safeguarding laboratory research and also recently Benedict et al (2018) on the management of gene drive arthropods in containment. Akbari et al., **(**2015) **"Safeguarding gene drive experiments in the laboratory"**, in *Science vol. 349 issue 6251*: http://science.sciencemag.org/content/349/6251/927 Benedict et al., (2018) "**Recommendations for Laboratory Containment and Management of Gene Drive Systems in Arthropods"** Vector Borne Zoonotic Dis. 2018 Jan 1; 18(1): 2–13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5846571/

[6] Akbari et al., (2015) "Safeguarding gene drive experiments in the laboratory", in Science vol. 349 issue 6251 http://science.sciencemag.org/content/349/6251/927

[7] World Health Organization (2014) **Guidance Framework for Testing Genetically Modified Mosquitoes** www.who.int/tdr/publications/year/2014/guide-fmrk-gm-mosquit/en/

[8] National Academies of Science, Engineering, and Medicine (USA) (2016) op. cit.

[9] James 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"** Am J Trop Med Hyg 98(6, Suppl):1-49. http://www.ajtmh.org/content/journals/10.4269/ajtmh.18-0083

[10] In addition, reports and decisions Informing the safe and responsible management of gene drive research have been published by, among others:

- Dutch National Institution for Health and Environment (RIVM), Netherlands (2016) **"Gene drives policy report"** https://www.rivm.nl/en/Documents_and_publications/Scientific/Reports/2016/februari/Gene_drives_Policy_report
- African Union decision July 2017 https://au.int/sites/default/files/decisions/33559-assembly_au_dec_642_-_664_xxix_e_1.pdf
- Australian Academy of Sciences 2017 op. cit.
- Haut Conseil des Biotechnologies, France (2017) " **Avis relatif à l'utilisation de moustiques GM dans le cadre de la lutte antivectorielle"** http://www.hautconseildesbiotechnologies.fr/fr/avis/avis-relatif-a-lutilisationmoustiques-gm-dans-cadre-lutte-antivectorielle
- Australian Office of the Gene Technology Regulator http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/amendment%20proposals-1

3 - New technological developments in synthetic biology since the last meeting of the Ad Hoc Technical Expert Group in December 2017

Research on gene drive is ongoing and the state of knowledge is growing rapidly. Some recent publications illustrate the advances in the scientific and technical ability to leverage gene drives to develop new tools to address conservation and public health issues; others also illustrate the critically important research work going into ensuring potential gene drive organisms can be used safely:

- A recent article published in Nature Biotechnology in September 2018 showed that laboratory populations of mosquitoes equipped with a gene drive can be suppressed within 11 generations. The research group demonstrated that a CRISPR–Cas9 gene drive targeting the doublesex gene from An.gambiae had successfully achieved complete population suppression in caged *Anopheles gambiae* mosquitoes. These proof-of-principle experiments translated a theoretical hypothesis into a potential genetic tool able to suppress the reproductive capability of the mosquito population[11]. The different components of the gene drive now need optimising to allow scaling up from a small lab cage population to the field, and this is likely to take several years.
- A research published in *Nature* in January 2019 detailed the successful use of gene drive in female mouse embryos to *"spread a modified gene through future generations*," representing the first successful use of a gene drive in mammals.[12] The focus of this paper was on how gene drives might be used in laboratory medical research, to make mouse models of particular human diseases more efficiently than is currently possible. As the authors acknowledge, the rates of drive will need to be increased substantially to make this approach potentially useful for rodent control.
- In a study published in January 2019 in *eLife*, researchers demonstrated how two molecular strategies can safeguard CRISPR gene drive experiments in the lab, without the worry of causing an accidental spread throughout a natural population.[13]. The study is another example of the efforts that scientists are doing on exploring safety mechanism to address potential concerns.

- Multiple papers have appeared showing how different types of gene drive will have different dynamics if released in the field, including male-drive-female-lethal drives[14], "tethered drives"[15] and allele-specific drives[16]. Dhole et al compare the expected dynamics of one locus under-dominant drives, 2 locus under-dominant drives, and daisy drives in a patch

[11] Kyrou et al., (2018) "***A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged Anopheles gambiae mosquitoes***" *Nature Biotechnology* **volume 36**, pages 1062–1066 https://www.nature.com/articles/nbt.4245
[12] Grunwald, *et al. (2019)* "**Super-Mendelian inheritance mediated by CRISPR–Cas9 in the female mouse germline**" Nature https://doi.org/10.1038/s41586-019-0875-2
[13] Champer, et al (2019) "**Molecular safeguarding of CRISPR gene drive experiments**" *eLife* https://elifesciences.org/articles/41439
[14] Burt, Deredec (2018) "**Self-limiting population genetic control with sex-linked genome editors**"**285***Proceedings of the Royal Society B: Biological Sciences* http://doi.org/10.1098/rspb.2018.0776
[15] Dhole et al. (2018) "**Tethered homing gene drives: a new design for spatially restricted population replacement and suppression**" bioRxiv 457564; https://www.biorxiv.org/content/10.1101/457564v4
[16] Sudweeks et al. (2018) "**Locally Fixed Alleles: A method to localize gene drive to island populations**" bioRxiv 509364; https://doi.org/10.1101/509364

model[17], and Champer et al. compare the expected dynamics of several under-dominant drives in continuous space[18].

- A special issue supplement of the Journal of Responsible Innovation 2018 included a suite of papers on The Roadmap to Gene Drives: Research and governance needs in Social, political and ecological context[19].

- Moro et al, 2018 looked a knowledge gaps for gene drive research to control invasive animal species, developing a model to support risk assessment for gene drive research, which aligns to the environmental risk assessment model suggested by the NASEM report on gene drives in 2016[20].

- Adelman et al., 2018 proposed a detailed review of potential standard operating procedures for contained laboratory gene drive research in disease vector mosquitoes while highlighting that containment measures need to be adapted on a case-by-case basis to the nature of the gene drive construct[21]. Similarly, Benedict et al. 2018 provided recommendations for containment and management of gene drive systems in arthropods[22].

- A late 2017 publication addressed the emergence of resistance to gene drive in a population that showed suppression of those same mosquitoes in laboratory cage experiments. The publication was the first documented example of selection for resistance to a synthetic gene drive, allowing important design recommendations and considerations in order to mitigate for resistance in future gene drive applications[23].
- Paul Neve published a perspectives article discussing the potential use of gene drive constructs for weed control, giving examples where gene drive is likely not to be appropriate, and others where it may be. He concludes that formal mathematical or computer modelling is needed to further assess whether any of these potential targets are worth following up[24].

Despite the advancement of the research in the laboratory, there has not yet been field tests or environmental releases of gene drive modified organisms. According to the current development

[17] Dhole et al (2018) "**Invasion and migration of spatially self-limiting gene drives: A comparative analysis**" *Evol Appl.* 11:794–808. https://doi.org/10.1111/eva.12583
[18] Champer, et al (2018) "**Population dynamics of underdominance gene drive systems in continuous space"** bioRxiv 449355; https://doi.org/10.1101/44935
[19] Special issue Journal of Responsible Innovation Volume 5, 2018: Roadmap to Gene Drives https://www.tandfonline.com/toc/tjri20/5/sup1?nav=tocList
[20] Moro et all, (2018) "**Identifying knowledge gaps for gene drive research to control invasive animal species: The next CRISPR step**" Global Ecology and Conservation Volume 13, January 2018, https://www.sciencedirect.com/science/article/pii/S2351989417302196,
[21] Adelman et all (2018). "***Developing standard operating procedures for gene drive research in disease vector mosquitoes"***. Pathogens and Global Health, https://doi.org/10.1080/20477724.2018.1424514
[22] Benedict et all (2018) **op. cit.** in the work already cited
[23] Hammond *et al*., (2017) "**The creation and selection of mutations resistant to a gene drive over multiple generations in the malaria mosquito"**. PLOS Genetics, https://www.ncbi.nlm.nih.gov/pubmed/28976972
[24] Neve, P. (2018) "**Gene drive systems: do they have a place in agricultural weed management?"** Pest. Manag. Sci., 74: 2671-2679. https://onlinelibrary.wiley.com/doi/full/10.1002/ps.5137

pathway for a tool to control malaria-carrying mosquito populations, the earliest submission for field testing of a gene-drive based tool is likely to be 2024, with several more years of testing and review before it could be considered for use in an integrated vector control strategy. Invasive mice investigations are on similar time frames.

4 - 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

The discussion on the regulatory status of some living organism developed through new developments in synthetic biology was frequently part of the debate in the last meeting of the conference of the Parties in November 2018. Similar discussions on whether all biotechnology techniques lead to the creation of an LMO are occurring also at national level. With reference to these specific discussion on organisms developed through new techniques of genome editing, **the network considers gene drives to be LMOs that can be managed under the Cartagena Protocol.**

Annex I

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