**Submission by Austria**

**in response to**

**SCBD Notification No. 2018-103 (14 December 2018)**

1. 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;

We regard the preliminary analysis prepared by the Executive Secretary in document SBSTTA/22/INF/17 as an adequate synthesis of the work on this matter, done by the AHTEG on synthetic biology during its two meetings (September 2015, December 2017). We think that with this analysis it has been sufficiently clarified that the topic of synthetic biology fulfills the criteria set out in decision IX/29, paragraph 12, and therefore should be regarded as a “new and emerging issue”. We suggest that the upcoming AHTEG reviews this document and finalizes the exercise on that basis to be submitted to SBSTTA.

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

Genome editing approaches (including highly multiplexed CRISPR-based methods and MAGE) may be used for large-scale engineering of metabolic pathways and networks, compare e.g. (Chari & Church 2017).

This may also be tried in plants, however the efficiency of multiplexed editing is still said to be quite low (reports at OECD 2018) and trade-offs vis a vis the frequency for off-target modification activity may impede the feasibility of such approaches.

Nevertheless proof-of-concept studies for multiplexed approaches with different site-directed nucleases were conducted in various crops, including maize (Qi et al., 2016), rice (Xu et al., 2016) and wheat (Wang et al., 2014; Gil-Humanes et al., 2017). In rice up to 21 different target genes were modified in a single step (Liang et al., 2016). In a recent study in wheat 35 different alpha-gliadin genes out of the 45 genes present in a wildtype line were knocked out using a multiplexed approach (Sanchez-Leon et al., 2018).

Other recent reports indicate that multiplexed genome editing to modify a few target loci only is sufficient to generate dramatic phenotypic changes in plants. Two recent publications (Li et al., 2018; Zsögön et al., 2018) indicate the potential of genome editing for an approach called de novo domestication, i.e. to rapidly develop crop lines from wild forms with desired properties like strong resistance towards pathogens or salt tolerance. In both cases relevant agronomic characteristics associated with domesticated tomato plants were established in different lines of *Solanum pimpinellifolium* by simultaneously editing only 4 or 6 genomic loci, respectively, while maintaining the desired resistance traits present in the wild lines. Among the introduced domestic characteristics were increased fruit number, size, shape and nutrient content of fruits as well as plant architecture and growth characteristics.

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Zsögön, A., Čermák, T., Naves, E.R., Notini, M.M., Edel, K.H., Weinl, S., et al. (2018). De novo domestication of wild tomato using genome editing. *Nature Biotechnology* 36**,** 1211. doi: 10.1038/nbt.4272

(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

Negative impacts on the environment and human health

Environmental impacts, including those on biodiversity, of organisms containing engineered gene drives (gene drive organisms; GDOs) are likely to occur if GDOs are developed that intentionally alter wild populations and are able to spread in an unlimited manner. The intended genomic changes have the potential to alter not only target populations and species but also non-target species, in case cross-breeding or hybridisation occurs between species. Gene flow between individuals and transfer of the gene drive mechanism together with cargo genes within a target population is the inherent and intended characteristic of all gene drive applications. Gene drive applications which aim at suppressing target populations of vector-transmitting mosquitoes may also affect related species, as hybridization and interspecific gene flow between different mosquito species have been documented. Also intraspecific hybridization within mosquito species is likely to be of relevance.

Due to the self-sustaining character of the edited genome in GDOs, evolutionary responses of organisms to the gene drive mechanism have been considered. The occurrence of resistance to gene drive applications is one of the most frequently discussed risks of this new technology. Resistance can compromise the functionality and effectiveness of the GDO and of the potential disease control strategy, in case human pathogen vectors are targeted. This may have profound implications for human health. Also long-term epidemiological consequences, e.g. due to altered virulence or transmission of pathogens to mosquitoes and humans have been predicted, as well as changes in the biology of the vector (e.g. host range, “vector-switching”). In addition, impacts on existing control strategies of pests or disease-carrying vector species may be relevant, such as a reduction of the conventional management efficacy. Biosafety risks of GDOs may be similar to those of other GMOs, however raising additional concerns due to their potentially unlimited spread through wild populations and ecosystems. Such risks refer to the complete eradication of species, negative impacts on non-target populations, other organisms and biodiversity. For example, food chain effects such as the loss of prey and important food sources for higher trophic levels may be relevant when applying suppression drives. Depending on the specific application, effects on predators, prey species, competitors or complex ecological functions may occur. The depletion of local or global populations of native and wild species communities, genetic diversity and changes in ecological interactions have been mentioned. Evolutionary responses may also refer to changes in mating systems of target plant populations as response to suppression drives. In particular, major ecological threats due to the unanticipated behaviour and uncertain effects of GDOs cannot be excluded if GDOs become invasive in wild populations.

Cultural and socioeconomic impacts

For releases of GDOs also other than environmental and human health implications have been discussed. The fact that GDOs can spread at long distances and across geographic regions implies that GDOs can potentially affect communities beyond the targeted release area. This triggered concerns regarding the regulation, governance, and control of GDO releases.  Scientists therefore call for an early and extensive involvement of stakeholders and local communities when releases are planned. Socio-cultural concerns and economic issues such as benefits and welfare impacts for GDOs have also been addressed, as well as implications for other types of agriculture, such as organic farming.

Literature

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(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.

A contentious case may be living organisms generated by multiplexed DNA free ZFN/TALEN/MN applications, which can be considered SynBio (see question b).

Such systems may be targeted to modify the genotype (through SDN-applications) or the phenotype by modification of gene expression through epigenetic mechanisms (through SDNs modified with domains that impact regulation of gene expression, repressors, positive transcription factors, or domains to introduce epigenetic modifications, e.g. methylases, demethylases, etc.)  (see e.g. Tycko 2017).

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