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| Paris, 17/03/2019 |
| NOTE DES AUTORITÉS FRANÇAISES |

**Objet** : **WPIEI - Biosécurité. Soumission de la France à la Notification 2019-009 de la Convention sur la diversité biologique/Protocole sur la biosécurité sur l'évaluation et la gestion des risques.**

**P. J.** : Soumission de la France en réponse à la notification 2019-009.

En complément du chapeau commun à l’Union européenne qui a été transmis au Secrétariat de la Convention sur la Diversité Biologique en réponse à la notification 2019-009, les autorités françaises prient la Présidence de trouver en pièce jointe la soumission complémentaire que la France adresse au SCDB sur cette même notification.

En réponse à cette même notification, la France propose en outre la nomination de deux experts :

Pour la participation au forum en ligne sur l’évaluation et la gestion des risques, institué par la décision CP-9/13 :

- Dr Catherine Golstein - Haut Conseil des Biotechnologies

Pour la participation au groupe d’experts, institué par la décision CP-9/13 :

- Pr Eric Marois - Université de Strasbourg.

**Contribution du HCB sur le forçage génétique**

15 mars 2019

1. *Experience in undertaking risk assessment of living modified organisms containing engineered gene drives and living modified fish (detailing how and for which cases); or else, lack of experience in doing so*

The Scientific Committee of HCB performed risk assessment of the gene drive-enabled mosquitoes described by Hammond *et al.* (2016) and Gantz et al. (2015), the first approach seeking population elimination, and the second, population modification – to make the mosquitoes incapable of pathogen transmission. Risk assessment was published in 2017 (HCB Scientific Committee, 2017). It was conducted in a comparative manner to risk assessment of other existing and emerging vector control techniques.

No work has been done so far on living modified fish.

Gantz, V.M., Jasinskiene, N., Tatarenkova, 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 *112*, 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*. Nat Biotechnol *34*, 78-83.

HCB Scientific Committee (2017). Scientific Opinion of the High Council for Biotechnology concerning use of genetically modified mosquitoes for vector control in response to the referral of 12 October 2015 (Ref. HCB-2017.06.07). (Paris, HCB), 142 pp. Available online: [http://www.hautconseildesbiotechnologies.fr](http://www.hautconseildesbiotechnologies.fr/).

1. *Challenges experienced or foreseen in undertaking risk assessment of living modified organisms containing engineered gene drives and living modified fish*

Challenges experienced during risk assessment of gene drive-enabled mosquitoes and foreseen in undertaking risk assessment of LMOs containing engineered gene drive include:

* The deliberate invasiveness of the desired modification, which in theory has the potential to reach all individuals of a species in the environment, whether to eradicate or to modify it.
* The probability of resistance evolution and its consequences

N.B. Because they operate through genetic targets, CRISPR-Cas-mediated gene drive techniques are conducive to resistance development, whether on account of pre-existing polymorphisms in the population or mutations induced by non-homologous end joining in the sequence recognised by the guide RNA. In the assessed cases, these developments could compromise the gene drive strategy or reduce gene drive efficacy, but would not result in any risks to health or the environment. However, we note that gene drive for the objective of population modification could theoretically encounter development of resistance to the desired phenotype after population modification, even if this possibility seems very unlikely in the case of the reported example of antibodies targeting *Plasmodium*. Technical developments might minimise the probability of resistance evolution.

* For CRISPR-Cas-mediated gene drive, the possibility of off-target cuts and their consequences

N.B. Cas9 collateral mutagenesis activity will not interfere with spread of a gene drive cassette but could generate off-target mutations. These mutations will generally be eliminated with a gene drive strategy for population elimination but could persist with a gene drive strategy for population modification. The possibility of undesirable mutations could be partly anticipated by preliminary studies in contained conditions. Nucleases less prone to collateral mutagenesis are being developed.

* The possibility of horizontal transfer and its consequences

N.B. Horizontal transfer of a gene drive cassette is possible, although highly unlikely on the scale of single individuals and generations. In most cases however, a gene drive cassette will not be functional after horizontal transfer to a new species.

* The possibility of vertical transfer to interfertile (sub)species and its consequences

N.B. Vertical transfer into interfertile related (sub)species is more probable than horizontal transfer. Extension of spread of a gene drive cassette to an interfertile related species can be planned and designed beforehand, if it is desirable, when the genomes of both species are known.

* Long term evolution of the gene drive system
* Assessment of the long-term impact in the environment
* The diversity of ecosystems that may be encountered
* The possibility of unintended replacement of the target species by another vector species, in case the gene drive seeks elimination of the target species
* The impossibility of undertaking field trials
* The need for modelling and for data required for modelling

1. *Specific needs (if any) to properly undertake risk assessment of living modified organisms containing engineered gene drives.*

Specific needs to properly undertake risk assessment of LMOs containing gene drive include:

* Effective containment of laboratory experiments
* Genome sequence of the target species
* Knowledge of interfertile species and their sequence at the gene drive site and potential homologous sites
* Knowledge of the potential genetic diversity of the target species at the target locus, to anticipate possible resistance development due to pre-existing polymorphisms, and assess its consequences in terms of risk
* Analysis of the endonuclease version used and the specificity of gRNAs employed in the target-species genome in order to assess the likelihood of collateral mutations and, where appropriate, estimate the consequences
* Knowledge of the bio-ecology and functional role of the targeted species and potential interfertile species with homologous sequence at the gRNA site in the different ecosystems that may be encountered
* Develop knowledge and procedures for assessing the gene-drive’s long-term effects on ecosystems
* Use of modelling to anticipate different scenarios for possible gene-drive’s evolutions in the environment
* Monitoring plan, that should follow the spread of the gene drive at a supra-national level
* Availability of strategies or antidotes for controlling the spread of gene drive, should monitoring data inform that it has some negative impact on health or the environment
* A plan for possible reversion to near wild-type situation following gene drive deployment