Comments on Perseus Report on Gene Drives

1. Comments, by page and line number

Page 3, Lines 1-2:

The sentence, “Gene drives allow for a trait to be distributed across generations deviating from the laws of Mendelian inheritance”, expresses a perspective that should be avoided in the discussion of gene drives, but also of genetic modification generally. There are no "laws" in biology, in the same sense as physical laws. However, accepting the terminology for the moment, gene drives and selfish genetic elements do not break them. For example, the “Law” of segregation is not broken by gene drives. Chromosomes, and the genes (including gene drive constructs) on which they reside, continue to pair during meiosis and segregate into gametes. The “Law” of independent assortment is not broken by homing drives, underdominance, and most meiotic drives. Chromosomes, and the genes on which they reside, continue to segregate independently from other chromosomes and their respective genes. This is an important point to note, because describing gene drives as deviating from the "laws" of Mendelian inheritance perpetuates the mistaken view that they are somehow "unnatural".

Gene drives are selfish elements, which are ubiquitous in eukaryote genomes. There seems to be no reason to characterize them or their effects as abnormal. Indeed, biased inheritance is quite ‘normal’. Hurst (2019) makes the case that “While absence of bias in segregation ratios was key to the understanding that selection as a force can matter, a century later focus has to some degree shifted to the possibility that biased segregation matters…”. Thus, Hurst (2019) supports the point that the discussion of gene drives should move away from charged characterizations of ‘drive’ as ‘abnormal’ or ‘law-breaking’ or even ‘exceptional’. Hurst (2019) suggests that what we currently think of as “the rule” (unbiased inheritance) may be the exception and that what we currently think of as the “exception” (biased inheritance) may actually be the rule.

Page 3, Line 4:

The phrase “…increase in frequency independent of external selection pressure”, is inaccurate. The extent to which a selfish genetic element increases in frequency will absolutely be a function of its fitness effects. To indicate that fitness effects are irrelevant is to misunderstand the genetics but, more importantly, it furthers the view that gene drives are unnatural.

Page 3, Line 33:

The statement that gene drives will trigger further genetic modification is misleading here because the process that will occur in nature is no longer an artificial process. It should be treated in a manner analogous to the way non-driving constructs are dealt with by most regulatory agencies in the world, i.e. that LMOs derived through the process of breeding are subject to the same approval as the original transformation event. Thus, an LMO that acquires a transgene via natural sexual reproduction would not be considered having been derived by a new genetic modification.

Page 4, Line 7:

It must be noted that research is ongoing to reduce this problem. The efforts to do this are noted in the report by Rudelsheim and Smets, (2018).

Page 4, Line 9; Page 25, Lines 25-27:

The report does not specify the implied harm component of the risk of unlinking the payload (effector) gene from the drive mechanism. If the two components are separated, there would be no spread of the effector (unless it confers a fitness advantage), and the LMO where this unlinking occurred would be no different from other LMOs. In fact, the intentional unlinking of gene drive components is a strategy that is contemplated for limiting the effects of a gene drive. Genomes naturally contain numerous types of DNA that are no longer functional but continue to persist. Thus, gene drive elements uncoupled from their payload sequences would be no different than any other such piece of DNA.

Page 4, Line 21:

Extinction of a species is a much publicized concern connected with the deployment of gene drives, but it is not helpful for risk assessment purposes to highlight this narrative and ignore the more likely scenarios that are the concern of researchers, which is that many factors may inhibit the success of a drive under real world circumstances, and therefore, extinction of the target species by gene drives cannot be presumed.

Page 4, Lines 25-29:

This illustrates the problem of not recognizing the many different gene drive architectures that are possible. Resistance issues are mostly connected with Cas9-based gene drives. Other types of gene drive do not necessarily have the same concern.

Page 5, Lines 18-23:

While adverse effects on the conservation and sustainable use of biodiversity have been raised as a hazard with certain LMOs with engineered gene drives, this again fails to acknowledge the different types of gene drive systems that have been proposed. Risk assessments should be done case by case. In this respect, gene drive organisms are no different from other LMOs. It should be noted that while concerns have been raised about LMOs, these concerns have not materialized.

Page 5, Line 41:

Outcrossing per se is not a harm. Once again, any effect would depend upon the specific gene in question. Furthermore, because the intended effects of a gene drive are dependent upon outcrossing, the question of what an acceptable level would be does not make sense in this context.

Page 18, Line 44:

Not all unidirectional systems are meiotic drives. Annex 3 of this report provides other examples.

Page 19, Lines 26-27:

The report should take into account James et al. (2018), which is intended to be a supplement to the WHO guidance, with a focus on low-threshold gene drives. The authors acknowledge that the WHO phased testing approach might not be suited to these types of drives.

Page 22, Line 34 and Page 23, Line 3:

Line 34 on page 22 states that *Wolbachia* is not strictly a gene drive, but Page 23, Line 3 characterizes the risk assessment of *Aedes egypti* containing *Wolbachia* as "…bearing a gene drive system". This inconsistency should be rectified. While from a regulatory perspective, *Wolbachia* has not been regulated as an LMO—and does not fit the Cartagena Protocol's definition of and LMO—the methodology used for the risk assessment of this system could serve as guidance for LMOs containing gene drives.

Page 24, Lines 29-30:

The introgression of gene drive constructs into other genotypes is no different than introgression of, for example, transgenes in plants into other genotypes, especially those that are intended to be released as open pollinated varieties. Those descendant genotypes would not be fully tested either, yet this situation does not present a major problem for risk assessors. The original transformation event, however, will be fully characterized, for gene drive LMOs in the same way as non-gene drive LMOs.

Page 24, Line 40:

The targeting of non-domesticated or wild species is not an inherent use of gene drives. Traditional genetic engineering methods could also be used on non-domesticated or wild species. For example, current applications of sterile insects derived through genetic engineering, such as pink bollworm or mosquitoes, or cabbage looper, are all non-gene drive LMOs targeting wild species. Conversely, while there are no current applications, there is no inherent property of gene drives that would prevent their being applied to domesticated species. Whether a domesticated or wild species, the comparator would continue to include the non-modified organism.

Page 25, Lines 4-6:

There are non-profit organizations as well as entities in various countries that are responsible for wildlife and land management that monitor and manage range and wild lands. Therefore, there is existing experience in risk assessments residing in these entities that could be accessed.

Page 25, Lines 39-40:

This narrow scope of ecosystem effects may not encompass issues of concern to certain stakeholders.

Page 26, Line 7:

Gene drives are not likely to be used as a stand-alone control method.

Page 26, Line 42:

The risk issues connected with the evolution of resistance (separate from the effect on efficacy) need to be elaborated. Resistance could also be considered a positive effect if one were concered to restrict the spread of a gene drive.

Page 30, Lines 9-10, 26:

This is a critical point regarding risk assessment for gene drive organisms and should be highlighted. The risk assessment methodology does not need to change, although there might be a lack of certain types of specific information necessary for conducting a robust risk assessment.

Page 30, Lines 42-47:

Other comments made in this analysis argue against these characteristics as distinguishing gene drive organisms from other LMOs. Furthermore, these points would all apply to every gene drive organism but would depend on the specific case.

Page 31, Lines 2-6:

Engineered gene drives are not unique in modifying pest species. As mentioned above, LMO pest species are currently the target of SIT approaches to controlling pest populations. Furthermore, biocontrol strategies present similar issues.

Page 42, Annex 2:

A representative of the Agence National de Biosecurite (ANB) from Burkina Faso is a glaring omission from the list of persons consulted for this report. That country has the most experience with LM mosquito applications and will likely be one of the first countries where gene drive mosquitoes will be deployed. Therefore, the views of the Burkina Faso ANB. A representative of Brazil’s CTNBio, which has experience with LM mosquitoes should also have been consulted.

2. References

Hurst, L. D. 2019. A Century of Bias in Genetics and Evolution. Heredity 123: 33-43. https://dx.doi.org/10.1038/s41437-019-0194-2.

James S., Collins F.H., Welkhoff P.A, Emerson C., H. Godfray H.C.J., Gottlieb M., Greenwood B., 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 (6_Suppl): 1–49. https://doi.org/10.4269/ajtmh.18-0083.

Rüdelsheim, P.L.J. and Smets, G. 2018. "Gene Drives: Experience with Gene Drive Systems That May Inform an Environmental Risk Assessment." COGEM Report CGM 2018-03. Netherlands Commission on Genetic Modification.