Comments on Perseus Report

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“Study on Risk Assessment Application of annex I of decision CP 9/13 to living modified organisms containing engineered gene drives”

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| Report | Comment |
| **Executive summary** |
| lines 2-3Gene drives allow for a trait to be distributed across generations deviating from the laws of Mendelian inheritance. | Gene drives cause abnormal inheritance patterns. In sexually reproducing species, this is observed as a deviation from Mendelian ratios. In non sexually reproducing species, or cytoplasmic factors such as mitochondria, Mendelian ratios do not exist, but biased inheritance does. For example, conjugative plasmids carry post-segregational killing systems that bias inheritance during reproduction. Cooper, T.F.; Heinemann, J.A. Postsegregational killing does not increase plasmid stability but acts to mediate the exclusion of competing plasmids. Proc Natl Acad Sci USA 2000;97:12543-12648Cooper, T.F.; Heinemann, J.A. Selection for plasmid postsegregational killing depends on multiple infection: evidence for the selection of more virulent parasites through parasite-level competition. Proc Roy Soc Lon B 2005;272:403-410The sentence could be corrected to better generalize the definition rather than just adopt a limited characterization from those developing gene drives for sexually reproducing species. Eg, “Gene drives allow for a trait to be distributed across generations deviating from the expectations of unbiased segregregation.” Or, the sentence could be qualified as: “Gene drives allow for a trait to be distributed across generations deviating from the laws of Mendelian inheritance which apply in the case of sexually reproducing species.”The latter “solution” is not preferable though. First, because it ignores the applications of gene drives in the vast majority of organisms on earth, those that do not rely on meiosis for reproduction at all or at some times (this includes viruses, all prokaryotes and many fungi and plants too). Second, it ignores relevant risk assessment issues when a species switches to apomixes. Heinemann, J.A. A typology of the effects of (trans)gene flow on the conservation and sustainable use of genetic resources. Background Study Paper. Rome: UN FAO; 2007; ftp://ftp.fao.org/ag/cgrfa/bsp/bsp35r1e.pdf |
| lines 3-4Active in sexually-reproducing species, they are powerful tools to “drive” a gene, *i.e.* increase its frequency, independent of external selection pressure. | As previous comment. Amend appropriately. E.g. “They can be active in both sexually and non-sexually reproducing…” |
| line 19Since gene drives are based on mating potential | Incorrect. They are only based on this in sexually reproducing organisms. For gene drives on plasmids or viruses, the issues are at least as complex and important and not limited by such barriers. |
| lines 25-29 (also section 4.4.1)Relating to resistance development The presence or development of resistance against an engineered gene drive system, will reduce its efficiency in the host population, but will also limit the potential impact. Resistance may also be used deliberately as part of a scheme aiming to confine the engineered gene drive to a limited geographical area or a certain time period. | Important: a resistance mechanism itself may achieve a fitness value that allows it to increase in frequency in environments with gene drives, potentially affecting the ecology of organisms that use the same genetic components, eg Cas9 nucleases, for other purposes.Thus, resistance mechanisms do not necessarily reduce impact. |
| lines 35-36Once released, there is a potential to disseminate across borders. Again, this is not a characteristic *per se* of gene drives, rather of the host organism. | Revise: characteristic of the vector whether that be a host organism that reproduces sexually or an infectious element, such as conjugative plasmid, that reproduces by horizontal gene transfer. |
| **Background** |
| lines 2-4 | Revise as per comments above. Also, what does “beyond Mendelian inheritance” mean? |
| lines 17-24 | They may be used in combination. A drive on a conjugative plasmid may be use to suppress the population of certain other plasmids or viruses while also spreading a new trait (e.g. antibiotic resistance). |
| line 32Gene drives come with a fitness cost for the hosting organism. | Not necessarily true. A CRISPR/Cas system used by a plasmid against a bacteriophage may both drive itself and provide a fitness advantage. |
| **Considerations for risk assessment** |
| line 12 | “human disease” includes those caused by mutation. I don’t think that this report means to suggest germline gene drives for such diseases. Preferable language would be either “infectious diseases” or “human and veterinarian medicine” |
| line 27 and Annex 4Although the gene drives are constructed in the laboratory, | Incorrect. This does not have to be the case. They can be constructed in the environment as well through topical applications. Heinemann, J.A.; Walker, S. Environmentally applied nucleic acids and proteins for purposes of engineering changes to genes and other genetic material. Biosafety Health 2019; <https://www.sciencedirect.com/science/article/pii/S2590053619300266> |
| lines 29-33 | Critically important point. Note that other technologies, such as reviewed in the reference in comment just above, can substitute for a gene drive and just create a drive. |
| line 40In contrast, gene drives target non-domesticated or wild species. | Revise: In contrast, gene drives can be used also on non-domesticated or wild species. |
| section 4.1.5 Managing a stepwise approach and 4.6 Perspectives | This section implies that experiments are the first stage of the process leading to future steps in R&D. The first step is obtaining social license for even contemplating the work, including the full and proper consultation with indigenous peoples. Then and only then would one consider whether or how to address scientific uncertainty.I therefore also feel that the quote from James and Tountas (2018) is out of place and misleading. There are many ways to reduce uncertainty that have nothing to do with promoting more scientific research. For example, it is possible that a hydrogen bomb could ignite the atmosphere. Prior to its first testing, it was uncertain what size of bomb would do so. The option taken was research and ultimately testing to see if the atmosphere would spontaneously ignite. That doesn’t mean it was the only option. At least one other was to abandon all interest in hydrogen bombs. The quote furthermore suggests that uncertainty lowering is the only possible outcome. It is not. |
| 4.3.2 Non-target organisms lines 10-12However, since gene drives are based on mating potential, the potential for exchange with related species is very species specific | Incorrect. This is the effect of having a flawed definition of a gene drive, one that is attached to only a particular kind of biology (organism reproduction, organisms that reproduce via a meiotic pathway, organisms with no cytoplasmically inherited elements…). Neither the vector, organism or biotechnology is confined to sexually reproducing organisms or strict species boundaries even if they are sexually reproducing. |
| section 4.5.1 lines 40-41This would limit the capacity of the gene drive to spread. | None of this is as certain as the sentence suggests. These have not been demonstrated outside of models and at best limited laboratory experiments. Suggest revising to:“This may in theory limit the capacity of the gene drive to spread.” |
| lines 42-43A CRISPR-based gene drive could also be used to block the spread of other gene drives by recoding 42 sequences targeted by the unwanted drive (‘immunising’ drive) | Same as above. Needs qualifying because it is not demonstrated with the certainty that the sentence implies. |
| **Informing the application of Annex I of decision CP-**1 **9/13** |
| section 5.1.3 lines 15-16a self-propagating gene drive application may require more stringent management considerations than the proposed self-limiting applications. | Note that often the text assumes some static state can be achieved. Eg., a low threshold drive will remain active; a drive with some mitigation feature will stay self-limiting. But nature isn’t static. What starts out as a self-limiting or resistance mechanism may also evolve. |
| lines 24-25 | Critically important point. Also illustrates that more research may not reduce uncertainty if a proper baseline is unachievable. |
| section 5.2 | Do any of the listed resources consider gene drives in cytoplasmically inherited elements, or partially or completely asexually reproducing organisms? If not, then existing guidance is incomplete. |