PNAS LETTER

"Target species complex" concept: Strengthening environmental risk assessment of engineered gene drives

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The recent opinion piece of Christophe Boëte critiqued the concept of the *target species complex* (TSC) in environmental risk assessment (ERA) of engineered gene drives (EGDs) (1). While constructive debate is essential, the piece misrepresents the purpose of TSC and conflates unrelated mechanisms, creating misconceptions that merit clarification.

Malaria-transmitting mosquitoes often belong to species complexes, comprising vector and nonvector species, where hybridization can be detected in laboratory settings and occasionally in the field (2–4). Low-threshold EGDs are self-sustaining and nonlocalizing (5). Should such EGD be released in a species complex where target genomic sequences are conserved, in the event of interspecific mating in the field vertical gene drive transfer (VGDT) to nonvector species could occur, potentially harming biodiversity protection goals. Conversely, VGDT to vector species could advance health objectives (6).

Proposed by Connolly et al. (6), TSC is a practical framework for ERA to distinguish intended and unintended consequences of EGD within species complexes, providing a systematic approach to explicitly identify and consider potential adverse effects on related species where VGDT may occur. Importantly, a number of caveats accompanied this TSC proposal, including i) the need to differentiate between the "mechanism" and "intention" of EGD, as mechanistic targets may not be intended ones, ii) that TSC should only be applied on a case-by-case basis depending on the nature of the species complex, and iii) that the biological consequences of EGD in a species complex, and the need for robust ERA, remain unchanged, regardless of whether TSC is used (6).

Boëte argues that TSC "risks reframing collateral impacts as intentional outcomes," thereby narrowing ecological and regulatory considerations, and "is unlikely to provide a safeguard" (1). To clarify, we have never claimed that TSC is a safeguard, it is an approach to provide clarity, robustness, and comprehensiveness in ERA, not to eliminate risk. Likewise, we have never suggested that mechanistic impacts of EGD should be disregarded. All risks, intended or unintended, must be explicitly assessed within the ERA. Suggesting otherwise misrepresents the intent and scope of TSC.

Boëte's opinion piece also links VGDT with horizontal gene transfer (HGT), which is mechanistically distinct from VGDT and occurs through nonreproductive pathways that are irrelevant to TSC. Any potential harm from HGT following EGD release would be addressed within existing ERA frameworks (5).

We believe expectations for ERA of EGD should match those for conventional vector control tools. For example, insecticides could affect i) noninfectious mosquitoes within vector species (7), ii) nonvector mosquito species (8), iii) vector species other than mosquitoes, such as fleas or sandflies (9), and iv) other nontarget insect species (10). By Boëte's own terms, such impacts would constitute "collateral damage" that is "openly accepted." Holding EGDs to stricter standards than other forms of vector control seems inconsistent to us.

In conclusion, TSC is not a safeguard but a tool to provide clarity, robustness, and comprehensiveness in ERA for EGD. We welcome continued discussion based on the biological evidence base to advance shared goals of safety and effectiveness in malaria vector control.

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ACKNOWLEDGMENTS. We thank Luke Alphey for useful discussion. J.B.C. is supported by a grant from the Gates Foundation and Coefficient Giving.

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Author contributions: J.B.C., Y.D., D.C.M.G., and J.R. wrote the paper.

Competing interest statement: J.B.C. is a member of the Target Malaria not-for-profit research consortium, which is exploring the use of EGD for malaria vector control (https://targetmalaria.org/). J.B.C. and Y.D. served as members of the Ad hoc Technical Expert Group (AHTEG) on risk assessment for the Cartagena Protocol on Biosafety to the United Nations Convention on Biological Diversity, which has developed guidance on risk assessment of engineered gene drive (5).

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Published March 30, 2026.

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