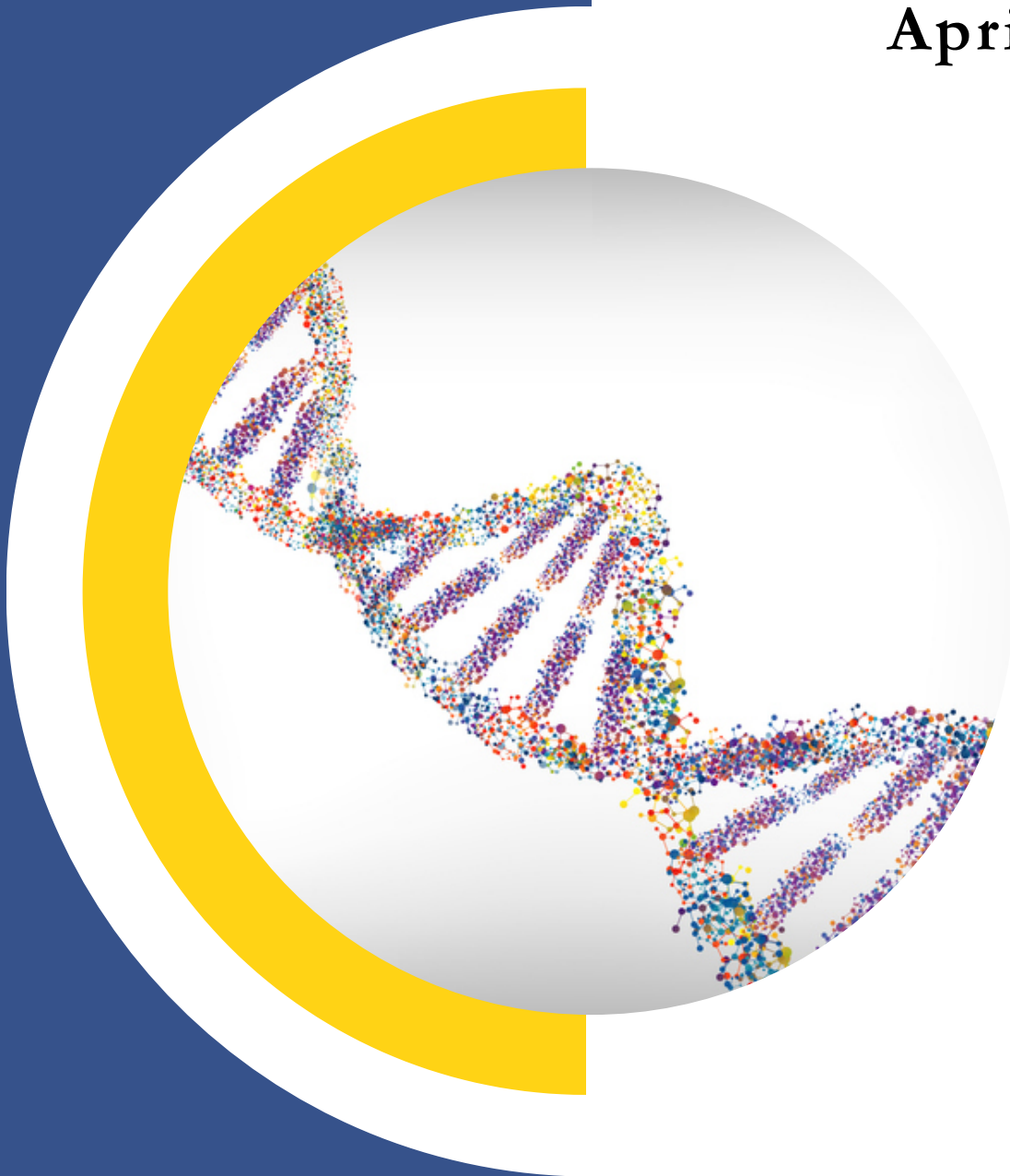


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Biosafety Considerations for Contained Research Involving Gene Drive Modified Organisms



National Institutes of Health
Office of Science Policy

Biosafety Considerations for Contained Research Involving Gene Drive Modified Organism

Background

Recent advances in gene drive technologies present opportunities for many life science applications with potential benefits to public health, agriculture, and the environment but also raise biosafety concerns. To help address issues associated with conducting research involving gene drive modified organisms (GDMOs) safely and responsibly, the National Institutes of Health (NIH) Director established the Gene Drives in Biomedical Research Working Group of the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC) and presented the following charge to the Committee:

- Consider whether existing biosafety guidance is adequate for contained laboratory research utilizing gene drive technology
- Outline conditions (if any) under which NIH could consider supporting field release of GDMOs.

The NExTRAC developed a report, [Gene Drives in Biomedical Research](#), in 2021 with recommendations for NIH to consider regarding contained research with GDMOs and conditions for potential field release. Following the release of the report, NIH amended the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* in April 2024 to strengthen existing biosafety policies and guidance by including specific considerations and requirements for conducting research involving GDMOs in contained research settings. Along with the *NIH Guidelines* amendments, the NIH Office of Science Policy developed this resource for Institutional Biosafety Committees (IBCs), biosafety professionals, and investigators to ensure the safe and responsible conduct of research involving GDMOs in a contained laboratory setting. NIH will continue to consider the additional NExTRAC recommendations; NIH does not currently support field release of GDMOs and the *NIH Guidelines* pertain to contained research.

IBC Requirements

Research subject to the *NIH Guidelines*, including research with GDMOs, requires review and approval by an IBC that is registered with the NIH Office of Science Policy prior to initiation. When the institution conducts research involving GDMOs, the institution must ensure that the IBC has adequate expertise (e.g., specific species containment, ecological or environmental risk assessment) using *ad hoc* consultants if necessary. In addition, when such research is being conducted, a Biological Safety Officer (BSO) shall be appointed to the IBC.

Risk Assessment Considerations

The conduct of risk assessments for research involving GDMOs presents challenges in addition to those associated with other genetically modified organisms (GMOs) or vectors because the

preferentially inherited traits of GDMOs spread and persist in the environment, are intended to modify natural populations, and may have associated impacts on the environment and society. The potentially broad and long-lasting impacts of the use of this technology on humans, other populations of organisms, and the environment are not seen with research involving clinical research participant cohorts or even with other GMOs not designed to survive outside of laboratory containment. As such, research involving GDMOs requires risk assessments that incorporate a broader scope of issues because of the greater uncertainty in terms of risks in the event of an unintended release from the laboratory.

Risk assessments for research involving GDMOs should consider:

- The specific types of manipulations based on
 - Function or intended function of the genetic/gene drive construct (i.e., a designed or engineered assembly of sequences)
 - Source of the genetic material (e.g., sequences of transgenes) in the construct
 - The modifications to the construct
 - Whether it is possible to predict the consequences of a construct, including the recognition of the potential to introduce an unintended gene drive (i.e., construct not specifically designed as a gene drive but nonetheless having properties of a gene drive) into the organism and the possible consequences of escape into the environment
 - The potential ability of the gene drive to spread or persist in local populations
- The types of scientific questions that need to be answered and what data are needed to facilitate the risk assessment
- Options for approaches to risk mitigation for specific risks in experiments or when dealing with a high degree of uncertainty about risks
- When to consider implementation of more stringent containment measures until sufficient biosafety data are accrued to support conduct of the research at a lower containment level.

The *NIH Guidelines* place biological agents into one of four Risk Groups, based on their ability to cause disease in humans. While Risk Groups (as defined in [Appendix B](#) of the *NIH Guidelines*) are only applicable to human etiological agents, the concept of types of categories of risk may be useful for the conduct of risk assessments for research with GDMOs. While it is not currently possible to define criteria to classify gene drive technologies into specific risk categories because the technologies to generate GDMOs are still emerging and uncertainty remains regarding effects on organisms and ecosystems, risk profiles can be developed based on the following considerations:

- Potential for spread of the GDMOs in the event of release into the environment
 - Presence of targeted gene in non-laboratory populations

- Whether the target gene is
 - not present, present with some frequency, or conserved in natural population(s)
 - essential to survival/reproduction
 - likely to transfer to non-target species
- The speed of reproduction of the modified organisms
- Potential for persistence in the environment
 - The likelihood resistance to the transgene will be selected for if introduced into a natural population
 - Whether the gene drive technology is designed to be self-limiting (i.e., have limited ability to spread outside of a given area – spatially and/or temporally)
 - How high a number of organisms would be expected to need to be released to result in spread of the trait throughout a population
- Potential for ecological consequences if organisms spread or persist and how any consequences can be evaluated in the event of an inadvertent release

Containment and Other Biosafety Considerations

Based on the risk assessment, determination of appropriate containment for specific gene drive research should consider physical containment designed for the species of GDMO along with the availability of appropriate biological or environmental risk mitigation strategies.

- Physical Containment

Research involving GDMOs shall be conducted at a minimum of Biosafety Level 2 (BL2), BL2-N (certain animals) or BL2-P (plant) containment. Based on the risk assessment of a specific research protocol, the IBC may require enhancements or a higher level of containment. Review and approval from NIH OSP are required to lower containment below the minimum specified in the *NIH Guidelines*.

Standards for containment facilities, laboratory design, containment equipment, and biosafety practices and procedures are described in the following documents:

- [World Health Organization Laboratory Biosafety Manual](#)
- [Biosafety in Microbiological and Biomedical Laboratories](#)
- [NIH Design Requirements Manual](#)

The above documents provide general containment standards that are applicable when conducting biomedical research. Gene drive research may be conducted in a broad range of species, and institutions may wish to consult containment guidance tailored to the specific species or type of organism utilized in a particular protocol. The following documents provide additional guidance for specific types of organisms:

- [Arthropod Containment Guidelines](#) (Version 3.2, 2019)
 - [Addendum 1 Containment Practices for Arthropods Modified with Engineered Transgenes Capable of Gene Drive](#) (2022)
 - [USDA Containment Guidelines](#) for arthropods, certain plants, snails, nematodes, etc.
 - Small animals- [Appendix G, NIH Guidelines](#)
 - Large animals- [Appendix M, NIH Guidelines](#)
 - Plants- [Appendix L, NIH Guidelines](#)
- Biological and/or Environmental Risk Mitigation Strategies

Consideration should also be given to the risk mitigation strategies employed in specific research. The ability to constrain the spread of a gene drive depends on specific molecular architecture, target organisms, conditions of release, local environments, availability of mitigation approaches, and social contexts.

Biological containment considerations

- In certain gene drive systems, the design of the gene drive itself serves as a biological risk mitigation strategy
 - Localized gene drive approaches that are designed to spread only in a temporally or spatially defined region may present a lower risk than non-localized approaches designed to spread through a population and persist (e.g., modification drive) or cause the population to decrease (e.g., suppression drive)

Environmental containment considerations

- Is the area surrounding the laboratory
 - geographically isolated?
 - an environment in which gene drive organisms are not able to survive (e.g., tropical organism in an arctic climate)?
 - genetically isolated (e.g., an area with no native organisms that could mate with non-native laboratory organisms)?

Additional Resources for Information about Gene Drive Technologies and Risk Assessments

- NIH Novel and Exceptional Technology and Research Advisory Committee. [Gene Drives in Biomedical Research](#)
- National Academies of Sciences, Engineering, and Medicine. [Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values](#). *National Academies Press*. 2016.
- Adelman et al. [Demystifying the risk assessment process for laboratory-based experiments utilizing invasive genetic elements: It is more than Gene Drive](#). *Applied Biosafety: Journal of ABSA International*. 2021.

- Akbari, et al. [Safeguarding gene drive experiments in the laboratory](#). *Science*. 2015.
- Adelman et al. [Rules of the road for insect gene drive research and testing](#). *Nature Biotechnology*. 2017
- Benedict et al. [Recommendations for Laboratory Containment and Management of Gene Drive Systems in Arthropods](#). *Vector Borne Zoonotic Diseases*. 2018.
- Krishnan and Gillum. [Gene Drive 101: A Basic Guidance Resource for Biosafety Professionals](#). *Applied Biosafety: Journal of ABSA International*. 2017.
- Adelman et al. [Developing standard operating procedures for gene drive research in disease vector mosquitoes](#). *Pathogens and Global Health*. 2017.
- [GeneConvene Global Initiative Virtual Institute](#) (Foundation for the National Institutes of Health resource with content on gene drives and genetic biocontrol)

**For further information about the requirements of the *NIH Guidelines*, please email:
NIHGuidelines@od.nih.gov.**