



October 6, 2023

Submitted Electronically to: <https://osp.od.nih.gov/proposed-amendments-to-the-nih-guidelines-for-research-involving-recombinant-or-synthetic-nucleic-acid-molecules-nih-guidelines/>

RE: Response to *Proposed Amendments to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* (88 FR 54332)

To Whom It May Concern:

We write to offer comments in response to NIH's request for comments on the [*Proposed Amendments to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules \(NIH Guidelines\)*](#) ("Proposed Amendments") that were published in the Federal Register on August 10, 2023. COGR is an association of over 200 public and private U.S. research universities and affiliated academic medical centers and research institutes. We focus on the impact of federal regulations, policies, and practices on the performance of research conducted at our member institutions, and we advocate for sound, efficient, and effective regulation that safeguards research and minimizes administrative and cost burdens.

COGR and its member institutions recognize the importance of ensuring that research involving recombinant and synthetic nucleic acid molecules is conducted in a safe and secure manner that addresses the unique risks posed by this type of research. Our institutions strive to adopt and promote effective practices in this area, and we appreciate and support NIH's issuance of the Proposed Amendments. In particular, we support those areas in which the Proposed Amendments that harmonize the NIH Guidelines' requirements with those of the [*Centers for Disease Control and Prevention's Biosafety in Microbiological and Biomedical Laboratories*](#)¹ (BMBL).

Our specific comments below set forth additional ways in which we believe that the Amendments could be further improved. These comments are organized under the sections of the NIH Guidelines to which they refer.

Section I-E-7

This section defines "gene drive" as a "technology whereby a particular heritable element biases inheritance in its favor, resulting in the heritable element becoming more prevalent than predicted by Mendelian laws of inheritance in a population over successive generations." This definition is too vague because it does not clearly define a gene drive's capabilities, and the qualifier regarding Mendelian laws of inheritance would not apply to many organisms (e.g., bacteria, viruses, single celled organisms). Additionally, the definition does not account for the ability of a genetic element

¹ 6th ed. (rev. June 2020).

to pass through sexual reproduction and seems to conflate genetically modified organisms (GMOs) with gene drive modified organisms (GDMOs), even though not all GMOs are GDMOs. We recommend that that NIH consider replacing the proposed definition with the following definition for “gene drive” that appears in the glossary of the National Academies of Sciences, Engineering, and Medicine 2016 publication [*Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*](#)²:

A gene drive is a system of biased inheritance in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced. Thus, the result of a gene drive is the preferential increase of a specific genotype, the genetic makeup of an organism that determines a specific phenotype from one generation to the next, and potentially throughout the population.

Further, we recommended that this definition distinguish between natural and synthetic, or “engineered” gene drives because while GDMOs are GMOs, not all GMOs are GDMOs, as some GMOs cannot reliably pass along their changed trait, and thus have a limited impact on the overall population.³ Additionally, the definition of gene drive must make clear that it only encompasses those circumstances and organisms (plants, animals, arthropods) in which a gene drive is created. Finally, to avoid incorrect conflation of GMOs and GDMOs, we suggest that the NIH Guidelines address GDMOs through a separate section devoted to them.

Without a change in the definition of “gene drive,” there is a potential for this Proposed Amendment to be over-interpreted to imply that all animals with a genetic modification must be housed at BL2.

Section III-D-4-c(3)

The proposed changes to this section state:

Experiments involving the generation or use of gene drive modified animals require a minimum of BL2 containment and are covered under III-D-8, Experiments Involving Gene Drive Modified Organisms.

Please see the above comments regarding the definition of “gene drive” under Section I-E-7. Additionally, containment practices may vary between vertebrate and invertebrate animals, including, and consideration should be given to this fact, including arthropod containment levels (ACLs).

Section III-D-8

The addition of Section III-D-8 is redundant because the Proposed Amendments already include the term “gene drive” in Sections III-D-4, III-D-5, and III-E-3. Further, the addition of this section

² The National Academies Press, <https://doi.org/10.17226/23405>.

³ See, Medina, R.F., Kuzma, J. Engineered and natural gene drives: mechanistically the same, yet not same in kind. *Nat Commun* 14, 5994 (2023). <https://doi.org/10.1038/s41467-023-41727-3>.

creates a situation in which gene drives may require classification under more than one section of the NIH Guidelines. For example, plants would require classification under both Sections III-D-5 and III-D-8, and animals would require classification under Sections III-D-4-c and III-D-8. If the goal of the Proposed Amendments is to capture all gene drive research, we suggest consolidating all organisms under Section III-D-8, or adding provisions on gene drives to Section III-D-1 and III-D-2 (if gene drives are a concern in these organisms) to make clear that gene drive modified organisms cannot be classified under Section III-E. Alternatively, as previously suggested, a separate section of the Guidelines devoted to gene drives could be developed.

Section III-E-3

This section states that it:

[C]overs experiments involving the generation *or use* of rodents in which the animal's genome has been altered by stable introduction of recombinant or synthetic nucleic acid molecules, or nucleic acids derived therefrom, into the germ-line (transgenic rodents). [*Emphasis added.*]

The addition of the phrase “or use” makes it unclear as to whether the NIH Guidelines’ current exemption under Appendix C-VII for the purchase or transfer of transgenic rodents that require BL1 containment remains in place or if all such transgenic rodents would be subject to Section III-E-3 under this proposal. We urge NIH to clearly state whether the exemption in Appendix C-VII remains or is being deleted, and if it is the latter, then we urge NIH to reconsider and retain the exemption.

Appendix B-II-D

COGR supports the reclassification of West Nile Virus and St. Louis encephalitis virus to RG2.

Conclusion

COGR and its member institutions appreciate the opportunity to comment on the Proposed Amendments, and we believe our recommendations will further improve the NIH Guidelines. Should you have any questions regarding these comments, please contact me or Kristin West, COGR’s Director of Research Ethics and Compliance at kwest@cogr.edu.

Sincerely,



Matt Owens
President