

Request for Public Comments on
Proposed Amendments to the NIH
Guidelines for Research Involving
Recombinant or Synthetic Nucleic Acid
Molecules (NIH Guidelines)

August 9, 2023 – October 10, 2023

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Submit date: 8/15/2023

I am responding to this RFI: On behalf of myself

Name: Jackson Champer

Name of Organization: Peking University

Type of Organization: University

Role: Scientific researcher

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

I am a gene drive researcher. Different gene drives have vastly different ability to spread. Zero-threshold unconfined drives such as homing drives should get similar treatment the that described in these guidelines. However, there may be some conditions where less stringent confinement would be warranted. Here are some possibilities:

1. The species does not live in the area around the lab where an accidental escape could occur.
2. The gene drive somehow could not spread effectively in wild populations, such as by use of incompatible insect strains or a synthetic DNA as its target site.
3. The gene drive is designed to be intrinsically self-limiting, such as a split drive.
4. The gene drive is designed to be intrinsically confined with an introduction threshold, below which the drive cannot spread.

2. Comment - NIH is seeking input on its proposals:

Submit date: 8/24/2023

I am responding to this RFI: On behalf of an organization

Name: Brinda Dass

Name of Organization: Foundation for the national institutes of health- Gene Convene Global Collaborative

Type of Organization: Other

Type of Organization-Other: NGO

Role: Scientific researcher

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

Section I-E. General Definitions

Section I-E-7.

Currently states-

“Gene drive” is defined 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 misleading in that gene drive in itself is not a technology and gene drives exist in nature regardless of biotechnology using such elements to drive cargo for defined purposes. Engineered gene drive is when this phenomenon is harnessed using biotechnology to achieve the biased inheritance of chosen sequences. We would prefer the definition be amended to read as “Engineered Gene Drive” and by extension “Engineered Gene Drive Organisms”. This would also be aligned with international terminology currently in use such as the United Nations Convention on Biological Diversity and the Cartagena Protocol on Biosafety. Please also note the definitions in the scientific articles referenced below.

Standardizing the definition of gene drive Luke Alphey et al. <https://doi.org/10.1073/pnas.2020417117>

A gene drive is a gene drive: the debate over lumping or splitting definitions. Stephanie L James et al. Nature Communications 2023 <https://doi.org/10.1038/s41467-023-37483-z>

Gene Drive: Evolved and Synthetic. Austin Burt and Andrea Crisanti. ACS Chem. Biol. 2018, 13, 2, 343–346 <https://doi.org/10.1021/acscchembio.7b01031>

Section II-A-3. Comprehensive Risk Assessment

States that-

Specific attention must be paid to risks of an unintended release from the laboratory and the potential impact on humans, other populations of organisms, and the environment.

Considerations for conducting risk assessments for research involving gene drive modified organisms might include:

d. Whether it is possible to predict the consequences of a construct, including the recognition of an unintended gene drive (i.e., construct not specifically designed as a gene drive but nonetheless having properties of a gene drive) and the possible consequences of escape into the environment;

e. The potential ability of the gene drive to spread or persist in local populations;

While there is definite value in conducting a risk assessment including potential ecosystem impacts

(with reference to Section V-N

Determination of whether a gene drive modified organism has a potential for serious detrimental impact on managed (agricultural, forest, grassland) or natural ecosystems)

as described above, there is concern as to the capacity of individual IBCs to take on such work on their own and the potential cost if consultants

(with reference to Section IV–B–2–a–(1).

When the institution conducts research involving gene drive modified organisms the institution must ensure that the Institutional Biosafety Committee has adequate expertise (e.g., specific species containment, ecological or environmental risk assessment) using ad hoc consultants if necessary.)

will be needed to provide the necessary depth of expertise and experience particularly where there is limited history of use and prior information. It would be helpful to point IBCs to existing guidance on ecological risk assessment conduct and reporting that would be considered acceptable.

2. Comment - NIH is seeking input on its proposals:

Uploaded File:

comments-to-FR-notice-on-NIH-Guidelines-changes-24-Aug-2023.docx

Email: bdass@fnihi.org

Section I-E. General Definitions

Section I-E-7.

Currently states-

“Gene drive” is defined 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 misleading in that gene drive in itself is not a technology and gene drives exist in nature regardless of biotechnology using such elements to drive cargo for defined purposes. **Engineered** gene drive is when this phenomenon is harnessed using biotechnology to achieve the biased inheritance of chosen sequences. We would prefer the definition be amended to read as “Engineered Gene Drive” and by extension “Engineered Gene Drive Organisms”. This would also be aligned with international terminology currently in use such as the United Nations Convention on Biological Diversity and the Cartagena Protocol on Biosafety. Please also note the definitions in the scientific articles referenced below.

Standardizing the definition of gene drive Luke Alpey et al. <https://doi.org/10.1073/pnas.2020417117>

A gene drive is a gene drive: the debate over lumping or splitting definitions. Stephanie L James et al.

Nature Communications 2023 <https://doi.org/10.1038/s41467-023-37483-z>

Gene Drive: Evolved and Synthetic. Austin Burt and Andrea Crisanti. ACS Chem. Biol. 2018, 13, 2, 343–346 <https://doi.org/10.1021/acscchembio.7b01031>

Section II-A-3. Comprehensive Risk Assessment

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Specific attention must be paid to risks of an unintended release from the laboratory and the potential impact on humans, other populations of organisms, and the environment.

Considerations for conducting risk assessments for research involving gene drive modified organisms might include:

d. Whether it is possible to predict the consequences of a construct, including the recognition of an unintended gene drive (i.e., construct not specifically designed as a gene drive but nonetheless having properties of a gene drive) and the possible consequences of escape into the environment;

e. The potential ability of the gene drive to spread or persist in local populations;

While there is definite value in conducting a risk assessment including potential ecosystem impacts (with reference to Section V-N

Determination of whether a gene drive modified organism has a potential for serious detrimental impact on managed (agricultural, forest, grassland) or natural ecosystems)

as described above, there is concern as to the capacity of individual IBCs to take on such work on their own and the potential cost if consultants

(with reference to Section IV–B–2–a–(1).

When the institution conducts research involving gene drive modified organisms the institution must ensure that the Institutional Biosafety Committee has adequate expertise (e.g., specific

species containment, ecological or environmental risk assessment) using ad hoc consultants if necessary.)

will be needed to provide the necessary depth of expertise and experience particularly where there is limited history of use and prior information. It would be helpful to point IBCs to existing guidance on ecological risk assessment conduct and reporting that would be considered acceptable.

Submit date: 9/5/2023

I am responding to this RFI: On behalf of myself

Name: Anthony A. James

Name of Organization: University of California, Irvine

Type of Organization: University

Role: Scientific researcher

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

Please see attached PDF.

2. Comment - NIH is seeking input on its proposals:

Please see attached PDF.

Uploaded File:

AAJames-comments-to-proposed-changes-to-NIH-gene-drive-2023-17178.pdf

Description: Specific comments to sections of the proposed changes.

Email: aajames@uci.edu

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institutes of Health (NIH) Office of Science Policy (OSP): Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

AGENCY: National Institutes of Health, HHS.

ACTION: Notice.

Comments:

Section I–E–7. “Gene drive” is defined 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 generation.

*This definition is misleading because gene drive in itself is not a technology. Gene drives exist in nature independent of biotechnology. As discovery scientists working in the area, we define gene-drive as any natural or synthetic phenomenon that results in the distortion of the inheritance ratios following meiosis in a diploid organism. Gene-drive is used most-commonly in this sense to refer to circumstances in which one of a pair of alternative forms of a gene (alleles) in a heterozygous or hemizygous parent is inherited preferentially by its offspring (James, 2005). The broader array of **Gene drive mechanisms** include genetic phenomena such as competitive displacement, reduced heterozygous fitness, ‘under-dominance’, homing endonucleases, meiotic drive and the now widely used Cas9/gRNA technology (Macias et al., 2017; Bottino-Rojas and James 2022). Others are based on the exploitation of infectious and infectious-like agents, which includes extracellular and intracellular symbiotic microorganisms, viruses and transposons that circumvent Mendelian patterns of inheritance. The approved biocontrol agents based on Wolbachia exhibit gene drive because they are inherited in excess of Mendelian ratios. A **gene-drive system** is the final synthetic gene drive-inducing genetic construct based on one or more of the naturally occurring or synthetic mechanisms (James, 2005).*

Bottino-Rojas, V. and James A.A. (2022). Population Modification Using Gene Drive for Reduction of Malaria Transmission. In: Transgenic Insects 2nd Edition. (eds) Benedict, M.Q. and Scott, M. CABI Wallingford UK, 243-258.

James, A.A. (2005) Gene drive systems in mosquitoes: rules of the road. Trends in Parasitology **21**, 64-67.

Macias, V.M., Jimenez, A.J., Burini-Kojin, B., Pledger, D., Jasinskiene, N., Phong, C.H. et al. (2017) nanos-driven expression of piggyBac transposase induces mobilization of a synthetic autonomous transposon in the malaria vector mosquito, Anopheles stephensi. Insect Biochem. Molec. Biol. **87**: 81-89.

Section IV–B–2–a–(1).

Committee prior approval. [] When the institution conducts research with gene drive modified organisms, the impact on ecosystems should be assessed by the Institutional Biosafety Committee (see Section V–N, Footnotes and References of Sections I– IV).

This should be necessary only if there is a chance of escape into and establishment in the local environment.

Section V–N

Determination of whether a gene drive modified organism has a potential for serious detrimental impact on managed (agricultural, forest, grassland) or natural ecosystems should be made by the Principal Investigator and the Institutional Biosafety Committee, in consultation with scientists knowledgeable of gene drive technology, the environment, and ecosystems in the geographic area of the research.

This should be necessary only if there is a chance of escape into and establishment in the local environment.

Appendix L–III–C–1.

Effective dissemination of arthropods and other small animals can be prevented by using one or more of the following procedures: (i) use non-flying, flight- impaired, or sterile arthropods; (ii) use non-motile or sterile strains of small animals; (iii) conduct experiments at a time of year that precludes the survival of escaping organisms; (iv) use animals that have an obligate association with a plant that is not present within the dispersal range of the organism; or (v) prevent the escape of organisms present in run-off water by chemical treatment or evaporation of run-off water.

The described confinement/containment conditions are impractical. Items i-iii prevent year-round laboratory maintenance of the gene-drive strains and preclude investigating important components of the strains (e.g. flight impairment precludes studying mating behavior of many insects, sterile animals prevent evaluating inheritance biases [how will you know you have a drive system?]). Akbari et al. (2015) developed a list of complementary confinement strategies that has been adopted by Institutional Biosafety Committees to allow safe and practical solutions to confinement (reproduced below). Most researchers use a combination of Molecular and Barrier confinement. Global warming may impact Ecological confinement, but that can be verified in the locale in which the experiments are being performed.

Potentially stringent confinement strategies for gene drive research		
Multiple stringent confinement strategies should be used whenever possible.		
TYPE	STRINGENT CONFINEMENT STRATEGY	EXAMPLES
Molecular	Separate components required for genetic drive Target synthetic sequences absent from wild organisms	sgRNA and Cas9 in separate loci (8) Drive targets a sequence unique to laboratory organisms (3,4,8)
Ecological	Perform experiments outside the habitable range of the organism Perform experiments in areas without potential wild mates	<i>Anopheles</i> mosquitoes in Boston <i>Anopheles</i> mosquitoes in Los Angeles
Reproductive	Use a laboratory strain that cannot reproduce with wild organisms	<i>Drosophila</i> with compound autosomes*
Barrier	Physical barriers between organisms and the environment •Remove barriers only when organisms are inactive •Impose environmental constraints •Take precautions to minimize breaches due to human error	Triply nested containers, >3 doors (6) Anesthetize before opening (6) Low-temperature room, air-blast fans Keep careful records of organisms, one investigator performs all experiments (6)
*An example of reproductive confinement would be <i>Drosophila</i> laboratory strains with a compound autosome, where both copies of a large autosome are conjoined at a single centromere. These strains are fertile when crossed inter se but are sterile when outcrossed to any normal or wild-type strain because all progeny are monosomic or trisomic and die early in development.		

Submit date: 9/12/2023

I am responding to this RFI: On behalf of myself

Name: Rebeca Rodrigues dos Santos Silva

Name of Organization: Membros do Institutional Biosafety Committee (IBC) do HCFMUSP

Type of Organization: Not applicable

Role: Member of the public

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

Como forma de contribuição, cito o plano de ação para experimentos e atividades utilizando a tecnologia do DNA recombinante, com uma proposta de “minimizar os riscos em atividades envolvendo a tecnologia do DNA recombinante”, de forma adequada e alinhada com todos envolvidos no mesmo meio, através dos seguintes passos.

Planejar: Analisar os procedimentos operacionais padrão e a partir deles planejar o experimento;

Fazer: Coloque as ações planejadas em execução;

Checar: Mensure os resultados das ações; Agir: Entenda e corrija o que não ocorreu como o planejado e padronize o que deu certo.

Para implementar essa medida, devemos manter todos envolvidos informados de forma clara e coerente.

Translation of comment as provided by Rebecca Rodrigues on 9/15/23:

As a form of contribution, I quote the action plan for experiments and activities using recombinant DNA technology, with a proposal to “minimize the risks in activities involving recombinant DNA technology”, in an appropriate way and in harmony with everyone involved. Half, through the following steps. Plan: Analyze standard operating procedures and use them to plan the experiment; Do: Implement planned actions; Verify: Measure the results of actions; Act: Understand and correct what didn't happen as planned and standardize what worked. To implement this measure, we must keep everyone involved informed in a clear and coherent way.

2. Comment - NIH is seeking input on its proposals:

Email: beca.denaro12@gmail.com

Submit date: 10/2/2023

I am responding to this RFI: On behalf of myself

Type of Organization: Nonprofit research organization

Role: Member of the public

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

Does "gene drive animal" mean all transgenic animals? For example, would transgenic mice now need to be housed at BL-2N? Please clarify the language in III-D. As written, this is not feasible and the risk for transgenic mice being housed at BL-2N is very low.

2. Comment - NIH is seeking input on its proposals:

Submit date: 10/2/2023

I am responding to this RFI: On behalf of myself

Name: Major Eldridge

Type of Organization: Not applicable

Role: Member of the public

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

I appreciate the new committee requirement. Having a gene drive expert on the committee is not only logical, but ensures the credibility of the Biosafety Committee.

2. Comment - NIH is seeking input on its proposals:

I think these are good additions. If changing the language is suggested by the scientific community majority, then I am for it. I am also a proponent for reclassifying WNV and SLEV.

Email: majoreldridge@tamu.edu

Submit date: 10/5/2023

I am responding to this RFI: On behalf of myself

Name: Jeffrey D. Cirillo

Name of Organization: Texas A&M University

Type of Organization: University

Role: Scientific researcher

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

- 1) Minimum containment is already addressed in existing NIH guidelines, so no changes are needed. The only time additional scrutiny would potentially be needed is when release into the environment is expected. Otherwise, the additional administrative burden and cost is not warranted.
- 2) Risk assessment guidelines are already outlined well within NIH and BMBL guidelines, making additional guidelines duplicative, confusing and unwarranted.
- 3) Changes to the IBC and BSO are not needed. Educational opportunities may be necessary if they do not understand the technologies involved, but that could be addressed by standard notification procedures from NIH within their guidelines. Adding a clear description of the issue and technologies involved into the NIH guidelines would suffice.

2. Comment - NIH is seeking input on its proposals:

1. This change seems reasonable, since systems is more broad than viruses and clarifies that not only viruses can be used and would fit within this category.
2. This seems like a very reasonable re-classification to finalize, particularly since this level of containment has already been approved at several institutions as the result of risk assessment.

Submit date: 10/5/2023

I am responding to this RFI: On behalf of myself

Name: Stephen J Libbuy

Name of Organization: Stephen Libby PhD Consulting LLC

Type of Organization: Other

Role: Member of the public

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

The changes and issues addressed in the proposal are all clear and appropriate.

2. Comment - NIH is seeking input on its proposals:

This clears up a lot of confusion for IBC members and reviewers.

The pointing to the BMBL6th edition for additional guidance is very appropriate. The NIH Guidelines do not address the specifics of laboratory safety.

Well Done!

Submit date: 10/6/2023

I am responding to this RFI: On behalf of an organization

Name: Andrea Ladd

Name of Organization: University of Wisconsin

Type of Organization: University

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

2. Comment - NIH is seeking input on its proposals:

Uploaded File:

IBC-comment_Proposed-changes-to-the-NIH-Guidelines_100623.pdf

Description: Attached is a letter from the University of Wisconsin-Madison Institutional Biosafety Committee.

Email: andrea.ladd@wisc.edu



Environment, Health and Safety

DIVISION OF FACILITIES PLANNING & MANAGEMENT
UNIVERSITY OF WISCONSIN-MADISON

To: National Institutes of Health Office of Science Policy

From: The University of Wisconsin-Madison Institutional Biosafety Committee

Re: Proposed changes to the *NIH Guidelines*

Date: October 6, 2023

We are writing to provide comments on the proposed amendment of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*, Federal Register Document Number 2023-17178, on behalf of the University of Wisconsin-Madison Institutional Biosafety Committee (IBC).

In general, the UW-Madison IBC does not take issue with any of the proposed changes to the *NIH Guidelines*. However, as drafted the proposed amendment is a missed opportunity to make additional changes that would significantly improve the effectiveness of the *NIH Guidelines*. We propose that the NIH Office of Science Policy consider two additional changes not currently included in the proposed amendment.

First, we propose that Section III-D-4 be amended to remove the requirement that the minimum containment level for any recombinant microbe being administered to any whole animal be set at BL2/BL2-N (BSL2/ABSL2). The administration of microbes that are risk group 2 and higher to animals already have minimum containment levels set under Section III-D-1, so this requirement only impacts the administration of recombinant risk group 1 microbes to animals. In practice, this means that Minor Action requests under Section IV-C-1-b-(2) must be submitted to request approval to perform what is often very low risk research at BL1/BL1-N (BSL1/ABSL1). This creates an unnecessary administrative burden without any improvement in safety. This proscriptive approach also goes against the entire premise of risk assessment upon which the *NIH Guidelines* are meant to be based. We propose instead that the IBC be allowed to set containment levels for recombinant risk group 1 microbes administered to animals according to their assessment of the risks associated with the microbe, specific recombinant modifications, and animal species involved.

Second, we propose that the *NIH Guidelines* be amended to address a barrier to veterinary animal research. Under the *NIH Guidelines*, research animals receiving recombinant materials may not be released unless approval has been granted by another federal agency with jurisdiction. This means a client-owned animal that is participating in a research study cannot go home again if it receives recombinant materials. While it is important to prevent the release of experimental recombinant materials and organisms into the environment and wild populations, this prohibition effectively disallows clinical trials with client-owned animals that are not actively regulated by the FDA or USDA. Importantly, this excludes animal clinical trials not intended for the development of human therapeutics that are not directly involved in commercialization of an animal biologic. These exclusions include proof of concept studies for

the development of animal therapeutics and compassionate use of experimental biologics in animals.

NIH employees have publicly acknowledged the “regulatory dead zone” created by the gap between the *NIH Guidelines* and what falls under the jurisdiction of other federal agencies, yet it is not clear that any steps have been taken to address this problem. Meanwhile, institutions that receive federal funding and are subject to the *NIH Guidelines* cannot participate in these studies. This excludes universities with robust veterinary and agricultural schools – often those best poised to successfully conduct such studies – from conducting important research that serves to protect and treat our pets, service animals, and livestock.

Examples of instances where UW-Madison researchers came up against this barrier include the compassionate use of a therapeutic melanoma vaccine for cancer treatment in dogs and compassionate use of experimental poultry vaccines to protect domestic falcons during an avian influenza outbreak. In some instances we have been able to work with other federal agencies to obtain clearances, but in other instances the process of navigating the gaps in jurisdiction became so arduous and time-consuming that the researchers withdrew, the studies never proceeded, and the potential benefits to domestic animal populations were lost.

This “regulatory dead zone” is created by the limiting language in the *NIH Guidelines* and could be addressed by amending the *NIH Guidelines* to specifically allow the use of client-owned animals for veterinary clinical trials with recombinant materials. We propose that a section be created to cover veterinary clinical trials involving client-owned companion, service, and agricultural animals. This new section would be analogous to Section III-C, which covers human clinical trials with recombinant materials. Section III-C sets a precedent for living subjects of research with recombinant materials that are not subject to containment or prohibition of release. As with human clinical trials, the potential for recombinant materials and organisms used in veterinary clinical trials to be released into the environment (e.g., through shedding) would be part of the risk assessment performed by the IBC prior to approval to ensure effective precautions are used to prevent exposure to the community or wild populations.

Thank you for your consideration.

Sincerely,



Jeri Barak, PhD
Chair, IBC
Professor, Plant Pathology
1630 Linden Drive
Madison, WI 53706
(608) 890-2581
jeri.barak@wisc.edu



Andrea N. Ladd, PhD, RBP (ABSA)
Biological Safety Officer
Environment, Health & Safety
21 N Park St.
Madison, WI 53715
(608) 263-9013 office
andrea.ladd@wisc.edu

Submit date: 10/6/2023

I am responding to this RFI: On behalf of an organization

Name: Rachel Hodges

Name of Organization: BioPhorum

Type of Organization: Other

Type of Organization-Other: Biopharmaceutical Collaboration

Role: Scientific researcher

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

2. Comment - NIH is seeking input on its proposals:

Uploaded File:

BioPhorum-feedback-NIH-draft-proposals-to-research-involving-nucleic-acid-molecules.pdf

Email: rachel.hodges@biophorum.com



Collaborative review and feedback on:

**NIH Draft Proposals – Guidelines for
Research Involving Recombinant or Synthetic
Nucleic Acid Molecules**

05th October 2023

Contact: Rachel.hodges@biophorum.com

**Connect
Collaborate
Accelerate™**

Introduction to BioPhorum

BioPhorum's mission is to create environments where the global biopharmaceutical and device industry can collaborate and accelerate its rate of progress, for the benefit of all. Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum's membership now comprises top leaders and subject matter experts from global biopharmaceutical manufacturers and suppliers, working in both long-established and new Phorums. They articulate the industry's technology roadmap, define the supply partner practices of the future, and develop and adopt best practices in drug substance, fill finish, process development and manufacturing IT. In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.

Introduction:

BioPhorum brought together 10 subject matter experts from 9 of our member companies (including Bayer) to review and discuss the *NIH Proposed Changes – Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*.

The opportunity to provide feedback on the proposed changes is welcomed by the subject matter experts.

Collective feedback is provided, split into 2 sections: with an initial general feedback section followed by a detailed table indicating observations and where this is situated within the draft guidance.

Comments are submitted on behalf of BioPhorum members by Rachel Hodges, BioPhorum Senior Global Change Facilitator, and can be contacted directly if there are any questions regarding this review (rachel.hodges@biophorum.com).

General overview / feedback

General feedback on the overall guidance can be seen below:

1. The document is quite difficult to read and comprehend in some sections. It is suggested that the guidance would be enhanced by having a separate section for the Gene Drive technology, for ease of the reader and those unfamiliar with this topic.
2. Although not in the scope of the proposed changes, it is questioned why a BSO is not assigned for BSL2 work, due to the inherent risks and gaps associated with BSL2 activities.

Detailed comments

In addition to the general feedback comments above, the following table contains four detailed comments observed by the review team. The first column indicates where the comment relates to in the guidance and the right-hand columns provide the specific comment, justification and the proposed changes to the guidance, as applicable.

Section	Comment and Justification	Proposed Changes to guidance
II-A-3	Although not in the scope of the proposed changes, please can the term 'industrial scale volumes' be clarified/defined, or suggest it is amended to common terminology 'large scale'.	Requested to include a definition of 'industrial scale volumes'.
III-D-4	First paragraph at the bottom of page 54336 to the top of page 54337 is quite difficult to read. It is suggested that it is simplified or spilt into two sentences. In addition, it should be made clear that the requirements only apply to gene drive technology in a research setting. It could also be resolved by removing gene drive requirements here and simply referring to III-D-8.	
III-D-8	Recommend additional references to gene drive are incorporated into this section.	
IV-B-2-a	It is suggested that the two sentences regarding research with gene drive modified organisms are presented together rather than splitting them with the sentence regarding when a BSO is required. This will avoid switching topics multiple times within the paragraph, enhancing readability.	When the institution conducts research involving gene drive modified organisms the institution must ensure that the Institutional Biosafety Committee has adequate expertise (e.g., specific species containment, ecological or environmental risk assessment) using <i>ad hoc</i> consultants if necessary. The impact on ecosystems should be assessed by the Institutional Biosafety Committee (see Section V–N, Footnotes and References of

		Sections I–IV). When the institution conducts recombinant or synthetic nucleic acid molecule research at BL3, BL4, or Large Scale (greater than 10 liters) or research involving gene drive modified organisms, a Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee (see Section IV–B–3, Biological Safety Officer).
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Submit date: 10/6/2023

I am responding to this RFI: On behalf of an organization

Name: Lesley Decker

Name of Organization: University of Washington

Type of Organization: University

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

2. Comment - NIH is seeking input on its proposals:

Our feedback is in the attached PDF. Thank you.

Uploaded File:

Univ-Washington_Feedback-on-2023-proposed-NIH-Guidelines-changes.pdf

Description: Our feedback is in the attached PDF. Thank you.

Email: ldecker@uw.edu



October 6, 2023

Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

To Whom It May Concern:

The University Washington (UW) is submitting comments in response to the August 10, 2023, notice in the Federal Registry inviting feedback on proposed revisions to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines). Our institution appreciates the effort to update the NIH Guidelines to encompass new research technologies and to harmonize with the current edition of the CDC's Biosafety in Microbiological and Biomedical Laboratories (BMBL). Our comments below present ways we believe the proposed changes could be further defined and how the NIH can support Institutional Biosafety Committee (IBC) review of such research.

Regarding the proposed changes to include oversight for gene drive modified organisms in which the NIH proposes to: (1) clarify minimum containment requirements for research involving gene drive modified organisms, (2) propose considerations for risk assessment, and (3) define additional institutional responsibilities regarding Institutional Biosafety Committees and biosafety professionals:

Overall, we support the inclusion of gene drive experiments and gene drive modified organisms in the NIH Guidelines. The proposed definition of gene drive in Section I-E is incomplete and not specific enough to clearly classify gene drive research. A more comprehensive definition of gene drive experiments and gene drive modified organisms is needed to minimize ambiguity and distinguish between similar experiments. The guidelines should include either a definition or a reference to a resource with a definition. To accompany this change, the NIH should provide technical training, publications, or other resources to aid in training of IBC members and biosafety professionals who will evaluate such research.

Regarding the proposed changes to (1) replace the term "helper viruses" with the broader term "helper systems" and (2) reclassify West Nile Virus (WNV) and Saint Louis Encephalitis Virus (SLEV) as risk group 2 agents for consistency with containment guidance provided in Biosafety in Microbiological and Biomedical Laboratories (BMBL), 6th edition:



We generally support the proposal to replace the term “helper viruses” with “helper systems.” Like above, the NIH should provide definitions or examples for “helper systems” to minimize ambiguity and provide technical training resources or references. We also support the proposal to reclassify WNV and SLEV as Risk Group 2 agents.

Summary of Comments and Recommendations:

- We are in support of the proposed changes to the NIH Guidelines.
- A more clear and specific definition of gene drive experiments and gene drive modified organisms is needed to minimize ambiguity and distinguish between similar experiments. The guidelines should include either a definition or a reference to a resource with a definition.
- Definitions or examples for “helper systems” should be provided to minimize ambiguity.
- Technical training, publications, or other resources would benefit IBC members and biosafety professionals.

Thank you for the opportunity to provide our feedback on this important revision of the NIH Guidelines.

Sincerely,

Jason Smith, PhD
Associate Professor of Microbiology
Institutional Biosafety Committee Chair
University of Washington
Phone: 206-685-6144
Email: jgsmith2@uw.edu

Lesley Decker, MS
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CC:
Katia Harb, Senior Director, EH&S, University of Washington, kharb@uw.edu
Jennifer Cabarrus, IBC Coordinator, EH&S, University of Washington, jc242@uw.edu

Submit date: 10/6/2023

I am responding to this RFI: On behalf of an organization

Name: Kristin West

Name of Organization: COGR

Type of Organization: Other

Type of Organization-Other: non-profit association

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

Please see attached letter for comments.

2. Comment - NIH is seeking input on its proposals:

Please see attached letter for comments.

Uploaded File:

signed-response-to-NIH-Guidelines-re-synthetic-molecules.pdf

Description: Comments from COGR re. Proposed Amendments to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

Email: kwest@cogr.edu



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

Submit date: 10/7/2023

I am responding to this RFI: On behalf of myself

Name: Randy A. Albrecht

Name of Organization: Icahn School of Medicine at Mount Sinai

Type of Organization: University

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

I thank the NIH for the opportunity to provide my personal comments on the proposed amendments to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines).

I am supportive of establishing BSL-2/ABSL-2 as the minimum containment requirement for research involving gene drive-modified organisms (GDMOs).

The proposed amendments should address Section IV-B-1-c of Section IV-B, Responsibilities of the Institution, of the NIH Guidelines. Section IV-B-1-c should be updated, correspondingly, to reflect the new requirement for a BSO in oversight of research involving GDMOs, which may be conducted at BSL-2/ABSL-2.

Section IV-B-3, Biological Safety Officer (BSO), of the NIH Guidelines should be amended to define the basic qualifications of the BSO consistent with the evolving landscape of life sciences research, such as research involving GDMOs, enhanced pathogens with pandemic potential, and gain-of-function research of concern (GoFRoC). Currently, The Laboratory Safety Monograph, A Supplement to the NIH Guidelines for Recombinant DNA Research, July 1978, set forth the basic qualifications of the BSO on page 192. The qualifications of the BSO should be updated and clearly described within the main body of the NIH Guidelines.

Section IV-B-3-b of Section IV-B, Biological Safety Officer (BSO), should be amended to require appointment of a BSO if it engages in recombinant or synthetic nucleic acid molecule research at BL2, BL3 or BL4. The landscape of life sciences research and translational biomedical research, specifically human gene therapy, that is conducted at BL2 is expanding. Gain-of-function or dual use research is not limited to research conducted at BL3 or BL4. The proposed changes to the NIH Guidelines stipulate that research on Gene Drive Modified Organisms (GDMOs) should be conducted at minimum at BL2. Requiring an institutional appointment of a BSO if it engages in recombinant or synthetic nucleic acid molecule research at BL2 would avoid potential gaps in oversight by the BSO and strengthen the role of the BSO in oversight of life sciences research.

The application of the NIH Guidelines should extend beyond life sciences research funded by the NIH. For example, the National Science Foundation endorses the NIH Guidelines and requires funding applicants to adhere to the NIH Guidelines. There are ongoing public policy discussions regarding the limitation of federal oversight of gain-of-function and dual use life sciences that is not funded by the U.S. Government. Extending the application of the NIH Guidelines to all research funded by the U.S.

Government would be consistent at least with federal oversight of gain-of-function and dual use life sciences research.

Currently, the PHS398 forms for NIH grant/contract applications document institutional oversight of Human Subjects Research and Vertebrate Animals by documenting approval dates and assurance numbers of the IRB and IACUC, respectively. However, there are no equivalent questions regarding institutional oversight by the IBC of proposed research that may involve use of recombinant DNA or synthetic nucleic acids, and the equivalent registration of the IBC with the NIH OSP. The potential gap in this oversight pertains to the likelihood that a NIH application contains preliminary data generated from life sciences research that likely required IBC approval. The current NIH practice is to require that the applicant include a biohazard/biosafety statement somewhere in the application and then inquire about the IBC approval status during the just-in-time notice of NIH award of funding. These practices are not consistent with the NIH Guidelines, do not ensure the IBC has reviewed and approved the research, and has potential to undermine the oversight authority of the IBC. Amending the NIH grant/contract application forms to capture IBC approval status at the time of application submission would strengthen institutional oversight of biomedical research. Furthermore, this amendment would be consistent with the potential changes to the Policies for Oversight of Dual Use Research of Concern (DURC) and the Potential Pandemic Pathogen Care and Oversight (P3CO) policy framework and proposed bottom-up approach to institutional oversight of gain-of-function research of concern (GoFRoC), Federal Register Document Number 2023-18906.

2. Comment - NIH is seeking input on its proposals:

Email: randy.albrecht@mssm.edu

Submit date: 10/9/2023

I am responding to this RFI: On behalf of an organization

Name: Rebecca Moritz

Name of Organization: American Biological Safety Association International

Type of Organization: Professional org association

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

2. Comment - NIH is seeking input on its proposals:

Uploaded File:

ABSA-Comments-GDMO-10.9.23.pdf



ABSA INTERNATIONAL

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ed@absaoffice.org

October 9, 2023

National Institutes of Health
Office of Science Policy

Please see the comments regarding the proposed Amendments to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) gene drive modified organism.

Specific to the part of the proposal dealing with gene drive modified organisms. NIH proposed to:

- 1) Clarify minimum containment requirements for research involving gene drive modified organisms
 - BL2 designated as the minimum containment requirements for research involving gene drive modified organisms (GDMOs) is a prudent approach.
 - The application of the NIH Guidelines should be expanded to remove the loopholes for research accountability and biosafety risk inherent in research conducted in this country or by scientists stationed in this country but conducting research outside the United States.
 - It would be helpful to define “gene drive” and provide examples of what technologies may be used such as CRISPR, Transposons, etc.
 - Clarify if a vector (i.e. viral vector) that carry a gene drive intended for a vertebrate animal would be considered a 'GDMO' under the new guidance.
 - Clarify if a viral vector includes cell line or if only components of the gene drive mechanism is present (these should be explicitly excluded) For example, CRISPR-Cas9 in a cell line should be regulated by NIH guideline but not consider GDMO while viral vector or transgenic mice carrying just gRNA would not be considered GDMO.
 - USDA issued an exemption in 2020 on plant research involving gene drives (<https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/regulatory-processes/exemptions-confirmations/exemptions-confirmations>). With the revision of the NIH Guidelines, these exempted plants might fall under regulation again as GDMOs, even if the same line could have been created using conventional techniques. Clarify whether the USDA or NIH holds regulatory purview in such cases?
 - While “Gene Drive” is defined, “GDMO” is not well defined. Does it include microorganism and organisms (plant & animals-vertebrate and non-vertebrate).

2) propose considerations for risk assessment

- The proposed revisions to Section II-A-3 Comprehensive Risk Assessment outline a prudent strategy for risk assessment considerations with regard to GDMO in contained lab environment.
- Consider including guided questions when doing the risk assessment which may help building a decision tree/flow map with minimum requirements; a few examples are provided here: What are the off-targeting effects? Which delivery system is being used? Is this a permanent modification? Are multiply genes being targeted in one construct? What are the potential risks to personnel for exposure to material or the resulting modified organism? What is the knowledge base of the investigators? Have you done a walk-thru of the spaces where the work will be conducted?
- II-A-3-1-(d) regarding: *"including the recognition of an unintended gene drive (i.e., construct not specifically designed as a gene drive but nonetheless having properties of a gene drive)"* - should be specified further that this is for constructs not specifically designed as gene drive but handled simultaneously as gene drive constructs.
- Additional considerations for risk assessment of activities involving GDMOs:
 - When does this become a biosafety issue? When the organism reproduces?
 - Define organisms – microorganisms or animals? Or both?
 - How will it be known if a particular gene will be passed to the offspring?
 - Provide examples of risk assessments in help document
 - How will this oversight be managed without unnecessary administrative burden?
 - When should this be reported to the IBC?

3) define additional institutional responsibilities regarding Institutional Biosafety Committees and Biosafety Officers

For Biosafety Officers:

- We support the formal appointment of BSO as a member of the IBC – this will require also amending Section IV-B-1-c of Section IV-B, Responsibilities of the Institution, on page 26, to address appointment of a BSO for research involving activities with synthetic or recombinant nucleic acids at BL-2/ABL2, BL-3/ABL3 or BL-4/ABL4
- requiring a BSO for research involving work in BL-2/ABL2
- define lines of authority and lines of communication between BSO, IBC, and laboratory members. Currently the BSO can be bypassed in the required communication lines and be unaware of the noncompliance at their institution.
- consider including the qualifications of the BSO previously included in The Laboratory Safety Monograph, A Supplement to the NIH Guidelines for Recombinant DNA Research, July 1978, set forth the basic qualifications of the Biological Safety Officer (BSO) on page 192.

The qualifications of the individual need careful consideration. Familiarity with the laboratory setting and the basic scientific techniques and manipulations common to biomedical research is important. Ideally, the person should have experience in working within a biomedical research setting. A technical background in basic microbiology and knowledge of biological safety techniques and practices, containment equipment, and engineering principles pertaining to the design and operation of facility safeguards are also important. The individual should be able to communicate effectively with technical, administrative, and support personnel.

- In addition to the background included in the Laboratory Safety Monograph from 1978, consider including knowledge of new technologies.
- Consider including what the BSO can do or not do when the NIH Guidelines are not followed at the institution. The reporting requirement lies in the IBC, IMO the BSO serve as a voting member and advisory role which is already defined.
- Requiring a BSO for all BSL-2 or higher work may result in quite a burden for clinical research lab. On the other hand, I can't imagine someone without biosafety knowledge able to decipher and apply the NIH

guidelines at any biosafety level. A compromise may be that BSO is required for “BSL2 or higher where NIH guidelines is applicable”.

For IBCs:

- language in Section IV may be updated to recognize that membership of an IBC should be appropriate for research under review by that IBC. Currently, an institution may have more than one registered IBC with the NIH.

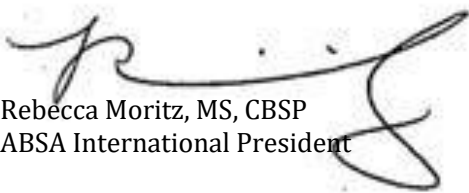
For example Section IV-B-2-a-(1) is proposed to be amended to read in part: *When the institution conducts recombinant or synthetic nucleic acid molecule research at BL3, BL4, or Large Scale (greater than 10 liters) or research involving gene drive modified organisms, a Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee **that reviews and approves such research***. For consistency, the phrase “that reviews and approves such research” or similar language would also need to be inserted in many places in Section IV with reference to a BSO for BL3, BL4, Large Scale, and GDMO.

No changes are being proposed in the FRN regarding field release research of GDMOs.

In addition, NIH is seeking input on its proposal to:

- 1) replace the term “helper viruses” with the broader term “helper systems.”; and
- it would be beneficial to add a definition/explanation of “helper systems” in the General Definitions to facilitate the scope of understanding this term’s application in the NIH Guidelines. Therefore, ensure that the term “helper systems” is explicitly defined in the NIH guidelines as it is in the CFR notice: (e.g., transient transfection systems, packaging cell lines, replicon systems, etc.)
 - consider using a different term than “helper systems”: The term “helper systems” is ambiguous and will likely lead to increased confusion in relevant literature as “systems” is used so widely. To avoid the confusion, distinct efforts to define this term in each guidance and scientific document could help to establish “helper system” as the specific term intended, however, it is less likely to gain the widespread recognition that “helper viruses” possesses. Consider use of alternative terms for “helper viruses” such as helper vehicles, assists, aids, modifiers, adaptors, devices, tools, etc.; Terms used in other disciplines to carry something distinct from the carrier, e.g., transportation, prosthetics, disability assistive devices.
 - consider the term “helper virus systems”, it would potentially alleviate the concern about what the helper is modifying while keeping the “system” to encompass the various components.
 - It would be helpful to provide definitions and examples regarding what a “helper system” is:
 - Is this still a virus or something else?
 - If a “helper system” is used, does it change the way the risk assessments are conducted?
 - If the update is trying to capture the helper plasmid and similar. Maybe the guideline should just spell that out.

Sincerely,



Rebecca Moritz, MS, CBSP
ABSA International President

Submit date: 10/9/2023

I am responding to this RFI: On behalf of myself

Name: Zach Adelman

Name of Organization: Texas A&M University

Type of Organization: University

Role: Scientific researcher

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

I support all of the indicated changes.

2. Comment - NIH is seeking input on its proposals:

I agree with the change in classification from "Helper viruses" to helper systems, as well as the reclassification of WNV and SLEV to RG2.

However, there seems to be a legacy mistake that has glided through the various editions of the NIH Guidelines for at least the past 40 years and should finally be corrected.

SLEV is listed under the Alphaviruses (Togaviruses). However, SLEV is not a member of this virus family. SLEV, like WNV, is a member of the family Flaviviridae, genus Flavivirus (now considered genus Orthoflavivirus).

<https://ictv.global/report/chapter/flaviviridae/flaviviridae>

Submit date: 10/9/2023

I am responding to this RFI: On behalf of an organization

Name: Sheryl Mansour

Name of Organization: University of California, San Diego

Type of Organization: University

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

The proposed addition of Gene Drive Modified Organisms (GDMO) into the NIH Guidelines provides guidance and instruction on institutional oversight and biosafety for research with an emergency technology that has a complex risk profile. Updates include specific requirements or expectations placed on the researcher, biosafety officer, IBC, and institution. Some of these expectations add complexity to the oversight mechanism, reduce the IBC's ability to conduct risk assessment based biosafety level determinations, and create more questions on how to appropriately implement the NIH Guidelines.

IBC's are aware of limitations to finding subject matter expertise in the field of gene drive. Additional clarity and guidance on selection of Ad Hoc reviewers will support institutions to supplement expertise when necessary. It is highly encouraged that the NIH OSP consider equity and access to Ad Hoc subject matter expertise for institutions of all sizes and research profiles.

2. Comment - NIH is seeking input on its proposals:

Can a definition of helper system be added into definitions Section of the NIH Guidelines? The Federal Register justification provided examples like "helper systems (e.g., transient transfection systems, packaging cell lines, replicon systems, etc.)". This will aid institutions in ensuring the helper system is evaluated appropriately under this section of the NIH Guidelines.

Uploaded File:

Complete_with_DocuSign_UCSD_Comments_for_NIH.pdf

Description: UCSD IBC Comments for NIH Office of Science Policy

Email: snmansour@ucsd.edu



INSTITUTIONAL BIOSAFETY COMMITTEE
ENVIRONMENT, HEALTH & SAFETY

9500 GILMAN DRIVE
LA JOLLA, CALIFORNIA 92093-0090

October 9, 2023

Office of Science Policy
National Institutes of Health
6705 Rockledge Drive Suite 750, MSC 7985
Bethesda, Maryland 20892-7985

REF: Comments for NIH Office of Science Policy

As committee members of the Institutional Biosafety Committee (IBC) who oversee the biosafety and biosecurity of U.S. government-funded research subject to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acids (NIH Guidelines)*, we are writing to provide our comments, questions, and concerns about the proposed updates to the NIH Guidelines described in the Federal Register, document number 2023-17178, citation 88 FR 54332. We appreciate this opportunity to comment on the August 2023 proposed NIH Guidelines updates from the NIH Office of Science Policy.

NIH Guidelines Proposal - GDMO: [\[excerpt from Comment Form\]](#)

Specific to the part of the proposal dealing with gene drive modified organisms. NIH proposed to:

- 1) clarify minimum containment requirements for research involving gene drive modified organisms
- 2) propose considerations for risk assessment
- 3) define additional institutional responsibilities regarding Institutional Biosafety Committees and Biosafety Officers

UCSD Comments:

The proposed addition of Gene Drive Modified Organisms (GDMO) into the NIH Guidelines provides guidance and instruction on institutional oversight and biosafety for research with an emergency technology that has a complex risk profile. Updates include specific requirements or expectations placed on the researcher, biosafety officer, IBC, and institution. Some of these expectations add complexity to the oversight mechanism, reduce the IBC's ability to conduct risk assessment based biosafety level determinations, and create more questions on how to appropriately implement the *NIH Guidelines*. The IBC has compiled comments, questions, and concerns on updates to specific sections:

- NIH Guidelines Section I-E:

Recommend adding the definition for a Gene Drive Modified Organism in Section I-E of the NIH Guidelines

- NIH Guidelines Section II-A-3:

In the risk assessment section of the proposed updates, what is considered biosafety data? Is it publications showing attenuated gene drives or safety data on the specific selected gene drive? Publications may not be available and institutions may want pilot projects to be performed by the researcher to provide biosafety data. Recommend inclusion of guidance for pilot projects that would provide biosafety data.

- NIH Guidelines Section III-D-8:

Some organisms and life stages of organisms would have greatly reduced risk of accidental release into the environment. Setting a minimum BSL reduces an institutions ability to perform a risk assessment based on the research, facility containment, etc. and determine an appropriate biosafety level. The broad range of possible targets for the creation of GDMO do not all warrant immediate assignment at BSL-2/N/P/AC.

Gene drive technology is advancing toward a more managed and control approach, improving safety and reducing risk to the environment. There are gene drives used to create GDMO where the drive is silenced or spliced out in future offspring or requires an unnatural mechanism to engage the gene of interest. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism and when the offspring would no longer meet the definition of GDMO. Clarification from the NIH on what is a GDMO is necessary as gene drive technology advances.

Will there be a process for downgrade requests to the NIH Office of Science Policy? A request for downgrade is described under Section III-D-4. Recommend adding this option to Section III-D-8.

- NIH Guidelines III-E-3:

Would this require that all offspring from GDMO be handled at ABSL-2? There are gene drives used to create transgenic mice where the drive is silenced or spliced out in future offspring. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism. Clarification from the NIH on what is a GDMO is necessary.

Recommend updating the FAQs for Research on Genetically Modified (Transgenic) Animals.

- NIH Guidelines IV-B-2-a-(1):

There are limited "Gene Drive" experts in the field and often at smaller institutions the 1 expert is the 1 PI submitting a gene drive BUA. Can the NIH provide clarity on Ad Hoc reviewers for an IBC? Does an Ad Hoc reviewer need to be local? What are the anticipated qualifications to be an Ad Hoc Reviewer?

- NIH Guidelines Section V-N:

Can the NIH provide clarity on Ad Hoc reviewers for an IBC? Many institutions will need to use an Ad Hoc. Does an Ad Hoc reviewer need to be local? What are the anticipated qualifications to be an Ad Hoc Reviewer?

- NIH Guidelines Section III-F-8 Appendix C-III-A:

This section will now require NIH exempt work with *Saccharomyces* and gene drive to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt at BSL-1 to now require IBC approval prior to start of work at BSL-2. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and BSL-1 when used as a gene drive modified organism?

- NIH Guidelines Section III-F-8 Appendix C-IV-A:

This section will now require NIH exempt work with *Saccharomyces* and gene drive to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt at BSL-1 to now require IBC approval prior to start of work at BSL-2. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and BSL-1 when used as a gene drive modified organism?

If implemented, the proposed updates to the *NIH Guidelines* would impede vital research efforts. Given the stringent biosafety regulations and thorough risk assessment by the IBCs, requiring a specific Biosafety Level for containment of GDMO, without a process for lowering the BSL based on risk, limits the ability of the IBC to operate as designed, and would also raise research costs and impede the cost-effectiveness of NIH-sponsored research.

IBC's are aware of limitations to subject matter expertise in the field of gene drive. Additional clarity and guidance on selection of Ad Hoc reviewers will support institutions to supplement expertise when necessary. It is highly encouraged that the NIH OSP consider equity and access to Ad Hoc subject matter expertise for institutions of all sizes and research profiles.

NIH Guidelines Proposal – Helper virus: [\[excerpt from Comment Form\]](#)

In addition, NIH is seeking input on its proposal to:

1. replace the term “helper viruses” with the broader term “helper systems.”; and
2. reclassify West Nile Virus (WNV) and Saint Louis Encephalitis Virus (SLEV) as risk group 2 agents for consistency with containment guidance provided in *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*, 6th edition.

UCSD Comments:

- NIH Guidelines Section: III-D-3 and III-E-1

Can a definition of helper system be added into definitions Section of the NIH Guidelines? The Federal Register justification provided examples like “helper systems (*e.g.*, transient transfection systems, packaging cell lines, replicon systems, etc.)”. This will aid institutions in ensuring the helper system is evaluated appropriately under this section of the NIH Guidelines.

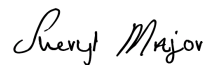
We thank you for your consideration of these comments, questions, and concerns.

Respectfully submitted,

Sincerely,



Aaron F. Carlin M.D. Ph.D.
Chair | Institutional Biosafety Committee
Associate Professor | Pathology and Medicine at
UC San Diego



Sheryl Mansour
Biosafety Officer | Institutional Biosafety
Committee
Environment, Health & Safety
UC San Diego

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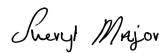
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Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	• Allow per session cookies

	• Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection
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** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time providing you with the revised hardware and software requirements, at which time you will have the right to withdraw your consent.

Acknowledging your access and consent to receive materials electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.

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Submit date: 10/9/2023

I am responding to this RFI: On behalf of myself

Name: Philip Barruel

Name of Organization: UC Davis

Type of Organization: University

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

Section I-E-7 – The definition of "gene drive" states, "a particular heritable element biases inheritance in its favor..." implies that the organisms have alleles for certain genes involved. Does the definition of "gene drive" exclude prokaryotes?

Section II-A-3 – The text, "The appropriate containment level may be equivalent to the Risk Group classification of the agent, or it may be raised or lowered as a result of the above considerations" seems to contradict the latter statement about minimum containment level as BL2. I acknowledge that this text is not new but the proposed changes to this section is in this context. It can be confusing if GDMO is read in this context.

Section II-A-3-3 – The reference to "more stringent containment measures" is vague. Do local IBCs have leeway to determine what "more stringent" means, or is there an acceptable definition for that term?

Section III-D-4 – Requires the minimum requirement of BL2 for gene drive modified animals. I realize this is referring to the NIH Guidelines "BL2-N" and not the BMBL ABSL-2. But from the perspective of BMBL (6th ed.) the key differences between ABSL-1 and ABSL-2 are biosafety cabinet and an autoclave in the ABSL-2 facility. Gene drive modified animal containment is not why a biosafety cabinet is recommended for ABSL-2, it is for when animals infected with Risk Group 2 microorganisms. Presence of an autoclave in the facility is not what is key to containment, it is having barriers that help keep escaped animals from escaping and appropriate inactivation of the gene drive modified animal (e.g., incineration of rodent carcasses).

Section III-D and III-E – A colleague mentioned that there are some gene drives that are used where the drive is silenced or spliced out in future offspring (whether animals or plants), please comment to verify that this "feature" takes these organisms outside of the definition of GDMO.

Section IV-B-1-c – This adds an IBC member for the GDMO area of expertise. Can this new IBC member be an ad hoc member who can be activated only when there's a GDMO IBC protocol under review? Also, can we use experts from a partner institution (regardless of distance from our institution)? It is possible that the IBC protocol submission is from the expert within our institution and this can create a conflict of interest. Having the ability to ask an expert in a partner institution provides a to address the conflict of interest.

2. Comment - NIH is seeking input on its proposals:

Email: prbarruel@ucdavis.edu

Submit date: 10/10/2023

I am responding to this RFI: On behalf of an organization

Name: Sepideh Sefidvash-Hockley

Name of Organization: Penn State University

Type of Organization: University

Type of Organization-Other:

Role: Member of the public

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

- Imperative all material must be submitted to the IBC regardless of the BSL level. (BSL 1, BSL 2, BSL 2+, BSL 3, BSL4). A campaign by all participating universities to ensure all faculty , post docs, etc. are aware of the need for a thorough review
- o Explicit SOP would also be required so a proper risk assessment can be completed by the scientific members of the committee, IBC Chair and Institutional Biosafety Officer
- Significant items to consider will be ;
- the working experience of staff manipulating the material
- Specific facility capabilities
- o Self-closing door
- o Sink with eyewash
- Properly certified BSC
- Properly maintained laboratory equipment.
- Initial Lab Survey/Inspection. Repeat annually or possible semi annually depending on the risk after the assessment
- o Complete understanding of decontamination and waste disposal process, as well as the spill and exposure response by the PI, the individual and the entire lab staff.
- o Each institution should also consider adding a specific section on their approval protocol specifically designed to focus in on the gene drive technology.

Section I-E-7 Clarity is needed on the definition of gene drives and gene drive technology IBCs and PIs have a better understanding of their roles and responsibilities. As written, the definition does not clearly define a gene drive's capabilities.

2. Comment - NIH is seeking input on its proposals:

- The changes regarding the helper system wording addition over helper virus seems like a good idea. The helper systems may stimulate the PI to provide all information regarding their project.

- The WNV and SLEV risk group upgrade also seems good so it is submitted appropriately by the PI. In these cases you would want to be "extra" sure you know the cradle to grave pathway of the material, especially if they are used in animals for expression. (transport, housing, waste handling, decontamination, waste disposal, spill and clean up, decontaminating equipment.

The risk assessment information within section 11_A-3, are defined enough so an acceptable assessments can be done.

Email: sqs7186@psu.edu

Submit date: 10/10/2023

I am responding to this RFI: On behalf of an organization

Name: Malissa Mayer-Diaz, MS, MSPH

Name of Organization: University of Texas Medical Branch

Type of Organization: University

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

For Part 1), regarding proposed changes to Section III-D-4, we welcome the clarification in the first paragraph that makes it obvious that "deliberate transfer of recombinant or synthetic nucleic acid molecules ...into whole animals" is covered in this Section.

For Part 1), regarding the proposed changes to Section III-E-3, we object strongly to the addition of the words "or use" to this Section, to read "This section covers experiments involving the generation or use of rodents ..." (emphasis added). There is no justification provided from the agency for the broadening of experiments covered by this Section. There is no risk assessment provided from the agency on why the use of transgenic rodents should be covered by the NIH Guidelines. The request for information does not even discuss this change to Section III-E-3, stating only "Section III-E-3 is proposed to be amended to reference the new Section III-D-8 to reinforce that research with GDMOs shall be conducted at a minimum of BL2." We understand that there are risks to personnel, the animal, the community, and the environment when generating transgenic rodents. We do not understand why the agency is proposing to expand Section III-E-3 to include the use of transgenic rodents.

2. Comment - NIH is seeking input on its proposals:

We are ambivalent on the change from "helper viruses" to "helper systems". If this proposed change is enacted, we would appreciate if the agency would either provide a definition for helper systems or keep the examples provided in the RFI: "However, helper systems (e.g., transient transfection systems, packaging cell lines, replicon systems, etc.) are more commonly used than a helper virus" (emphasis added).

We welcome the harmonization of the risk group for WNV and SLEV in the NIH Guidelines to the containment guidance provided in the BMBL. We expect that this will reflect the required safe handling of these agents. We expect this will reduce administrative burden for our investigators who would like to work with recombinant versions of these agents and currently require NIH approval to work with them at BSL2.

Email: fcblum@utmb.edu

Submit date: 10/10/2023

I am responding to this RFI: On behalf of an organization

Name: Leah Buchman

Name of Organization: Biotechnology Innovation Organization

Type of Organization: Professional org association

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

2. Comment - NIH is seeking input on its proposals:

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BIO-Comments_NIH-Proposed-GDMO-Research-Guidelines_-Final.pdf

Email: lbuchman@bio.org



Biotechnology Innovation Organization
1201 New York Ave., NW
Suite 1300
Washington, DC, 20005
202-962-9200

October 10, 2023

Office of Science Policy
Office of the Director
National Institutes of Health

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: Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

Introduction

The Biotechnology Innovation Organization (BIO) submits these comments in response to the National Institutes of Health (NIH) request for comment and public input on a proposal to revise the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) to include specific considerations and requirements for research involving gene drive modified organisms (GDMOs) in contained research settings.¹

BIO is the world's largest bioscience trade association representing roughly 1,000 biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products. BIO represents many academic, industrial, and scientific entities that are engaged in research activities involving recombinant and synthetic nucleic acid molecules.

BIO supports the efforts of NIH to ensure continued responsible research involving GDMOs in contained research settings by updating the guidelines applicable to research involving recombinant and synthetic recombinant nucleic acid molecules to expressly include considerations and requirements that will apply to research involving GDMOs in contained laboratory settings. BIO would be pleased to answer

¹ *National Institutes of Health (NIH) Office of Science Policy (OSP): Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*, 88 Fed. Reg. 54332 (Aug. 10, 2023).



any questions that NIH may have on the comments below, or to follow up in any manner that would be useful to NIH as it develops the revised NIH Guidelines.

NIH's Proposed Amendments to the NIH Guidelines

NIH proposes to amend the NIH Guidelines, in part, as follows:

- (1) clarify minimum containment requirements for research involving GDMOs;
- (2) propose considerations for risk assessment; and
- (3) define additional institutional responsibilities for Institutional Biosafety Committees (IBCs) and Biosafety Officers (BSOs).

In addition to these proposed amendments related to research involving GDMOs in contained laboratory settings, NIH also proposes to:

1. replace the term "helper viruses" with the broader term "helper systems"; and
2. reclassify West Nile virus (WNV) and St. Louis Encephalitis virus (LEV) as Risk Group 2 agents, to ensure consistency with containment guidance provided in the Biosafety in Microbiological and Biomedical Laboratories (BMBL), 6th edition.²

BIO's Comments

As an initial matter, BIO makes the general comment that it would be useful for NIH to define "containment" and "contained research" as these terms are used in the Notice and in the NIH Guidelines. BIO recognizes that these terms have generally understood meanings in the research community. However, as the Novel and Exceptional Technology Research and Advisory Committee (NExTRAC) noted in its 2021 report ("Gene Drives in Biomedical Research Report"; hereinafter, "NExTRAC Report"), it is important that terms be clearly defined, in order to promote common understanding.³ The NExTRAC Report specifically defined both "containment" and "contained research."⁴ BIO recommends that NIH should explicitly define these terms as set forth in the NExTRAC Report in the "Supplementary Information" section of the Notice,⁵ and that these definitions should be included in the revised NIH Guidelines.

² *Id.* at 54333.

³ NExTRAC Report at 7.

⁴ NExTRAC Report at 51-52.

⁵ 88 Fed. Reg. at 54333.



BIO respectfully submits the following comments to aspects of NIH's proposed amendments to the NIH Guidelines:

I. Definition of "gene drive"

NIH proposes to add a definition of "gene drive" to the NIH Guidelines. "Gene drive" is proposed to be defined 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."⁶

BIO Comment:

BIO notes that this definition of "gene drive" is consistent with the definition set forth in the NExTRAC Report and BIO concurs with the addition of this definition to the NIH Guidelines.

II. Revised Section II-A-3

The following text is proposed to be added to Section II-A-3 of the Guidelines:

Research involving gene drive modified organisms may require risk assessments that incorporate a broader scope of considerations because of greater uncertainty of the technology and potential uncertainty of the impact of the newly modified organism. Specific attention must be paid to risks of an unintended release from the laboratory and the potential impact on humans, other populations of organisms, and the environment.

Considerations for conducting risk assessments for research involving gene drive modified organisms might include:

1. The specific types of manipulations based on:
 - a. Function or intended function of the genetic/gene drive construct (i.e., a designed or engineered assembly of sequences);
 - b. Source of the genetic material (e.g., sequences of transgenes) in the construct;
 - c. The modifications to the construct;
 - d. Whether it is possible to predict the consequences of a construct, including the recognition of an unintended gene drive

⁶ *Id.*



- (i.e., construct not specifically designed as a gene drive but nonetheless having properties of a gene drive) and the possible consequences of escape into the environment;
- e. The potential ability of the gene drive to spread or persist in local populations;
 2. Options for approaches to risk mitigation for specific types of risks in experiments or when dealing with a high degree of uncertainty about risks;
 3. Considerations for implementing more stringent containment measures until biosafety data are accrued to support lowering containment.⁷

BIO Comments:

BIO in general concurs with the addition of this text to Section II-A-3 of the NIH Guidelines. BIO concurs with the conclusion that risk assessment applicable to GDMOs may be fundamentally different than risk assessments performed in other contexts. The potential for rapid irreversible population-wide genetic alterations that may result from field applications of gene drive technology is distinct from other technologies.

BIO concurs also with the inclusion of the considerations that should be included generally in risk assessment for research involving GDMOs as set forth in the NExTRAC Report at 14-15.

III. Revised Section III-F-1

Section III-F-1 of the Guidelines is proposed to be revised as follows:

Those synthetic nucleic acids that: . . . (2) are not designed to introduce a stable genetic modification, and . . .⁸

BIO Comment:

BIO concurs that advancements in genetic technologies have altered the scope and capabilities of genetic research and that this revision is appropriate in the context of current research efforts.

⁷ 88 Fed. Reg. at 54335.

⁸ *Id.*



IV. Establishing minimum containment requirements for GDMO research

NIH proposes that the Guidelines be revised to require that experiments involving GDMOs in contained research settings be conducted at a minimum of BL2 containment. Specifically, the Guidelines are proposed to be revised by adding new section III-D-8, and revising sections III-D-4, III-D-5, and III-E-3.

1. New Section III-D-8 is proposed to be added and to read as:

Section III–D–8. Experiments Involving Gene Drive Modified Organisms

Experiments involving gene drive modified organisms generated by recombinant or synthetic nucleic acid molecules shall be conducted at a minimum of Biosafety Level (BL) 2, BL2–N (Animals) or BL2–P (plant) containment.⁹

BIO Comment:

BIO agrees with the proposed addition to the Guidelines. BIO notes that this change is consistent with the recommendation of the NExTRAC Report at 13 and 16. BIO agrees with the proposal that experiments involving GDMOs in contained research settings should be conducted at a minimum of BL2 containment.

2. Section III-D-4 is proposed to be revised by adding the following four instances of new text:
 - i. This section covers experiments involving deliberate transfer of recombinant or synthetic nucleic acid molecules, DNA or RNA derived from recombinant or synthetic nucleic acid molecules, or recombinant or synthetic nucleic acid molecule-modified microorganisms into whole animals and experiments involving whole animals in which the animal's genome has been altered by recombinant or synthetic nucleic acid molecules, or nucleic acids derived therefrom, into the germ-line (transgenic animals). Experiments involving gene drive modified animals or experiments involving viable recombinant or synthetic nucleic acid molecule-modified microorganisms, except for viruses that are only vertically transmitted, may not be conducted at BL1–N containment. A minimum containment of BL2 or BL2–N is required (see Section III–D–8).

⁹ 88 Fed. Reg. at 54337.



- ii. (e.g., a gene drive; refer to Section III-D-8).
- iii. Experiments involving gene drive modified animals generated by recombinant or synthetic nucleic acid molecules shall be conducted at a minimum of BL2 or BL2-N (see Section III-D-8).
- iv. Section III-D-4-c-(3). 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.¹⁰

BIO Comment:

BIO concurs with these proposed revisions to the NIH Guidelines.

3. Section III-D-5 is proposed to be revised by adding the following new text:

Experiments involving the generation or use of gene drive modified organisms require a minimum of BL2 containment and are described under Section III-D- 8, Experiments Involving Gene Drive Modified Organisms.¹¹

BIO Comment:

BIO concurs with this proposed revision to the NIH Guidelines.

4. Section III-E-3 is proposed to be revised by adding the following new text:

Only experiments that require BL1 containment are covered under this section; experiments that require BL2, BL3, or BL4 containment are covered under Section III-D-4, Experiments Involving Whole Animals or *Section III-D-8, Experiments Involving Gene Drive Modified Organisms*.¹²

BIO Comment:

BIO concurs with this proposed addition to the NIH Guidelines.

V. Institutional responsibilities for IBCs and BSOs

¹⁰ *Id.*

¹¹ *Id.*

¹² 88 Fed. Reg. at 54338.



NIH proposes to alter requirements related to Institutional Biosafety Committees (IBCs) and Biosafety Officers (BSOs). Specifically, text related to GDMOs is added to Sections IV-B-1-c and IV-B-2-a-1; Section IV-B-3-a is revised to require that the BSO be a member of the IBC; Section IV-B-3-c is re-written to require a BSO for GDMO research; and the current IV-B-3-c is unchanged, but is re-lettered as IV-B-3-d.

1. Section IV-B-1-c is proposed to be revised by adding the following new italicized text:

Section IV-B-1-c. Appoint a Biological Safety Officer (who is also a member of the Institutional Biosafety Committee) if the institution: (i) conducts recombinant or synthetic nucleic acid molecule research at Biosafety Level (BL) 3 or BL4, (ii) engages in large-scale (greater than 10 liters) research *or (iii) conducts research involving gene drive modified organisms*. The Biological Safety Officer carries out the duties specified in Section IV-B-3.¹³

BIO Comments:

BIO concurs with the addition of the new italicized text.

In addition, BIO recommends the following revisions: For research that is conducted at BL3, BL4, and Large Scale, or that involves GDMOs, references to the IBC should specify “for the IBC that reviews and approves such research”. BIO recommends this change because a given institution may have more than one registered IBC with the NIH.

2. Section IV-B-2-a-1 is proposed to be revised by adding the following italicized new text:

When the institution conducts research involving gene drive modified organisms the institution must ensure that the Institutional Biosafety Committee has adequate expertise (e.g., specific species containment, ecological or environmental risk assessment) using ad hoc consultants if necessary. When the institution conducts recombinant or synthetic nucleic acid molecule research at BL3, BL4, or Large Scale (greater than 10 liters) or research involving gene drive modified organisms, a Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee (see Section IV-B-3, Biological Safety Officer). When the institution conducts research with gene

¹³ *Id.*



drive modified organisms, the impact on ecosystems should be assessed by the Institutional Biosafety Committee (see Section V–N, Footnotes and References of Sections I– IV). When the institution participates in or sponsors recombinant or synthetic nucleic acid molecule research involving human research participants, the institution must ensure that the Institutional Biosafety Committee has adequate expertise and training (using ad hoc consultants if necessary). Institutional Biosafety Committee approval must be obtained from the clinical trial site.¹⁴

BIO Comments:

BIO concurs with the addition of the new italicized text. As noted above, BIO recommends that references to the IBC should specify “for the IBC that reviews and approves such research”.

3. Section IV-B-3-a is proposed to be revised by adding the following italicized new text:

Section IV–B–3–a. The institution shall appoint a Biological Safety Officer if it engages in large-scale research or production activities involving viable organisms containing recombinant or synthetic nucleic acid molecules. *The Biological Safety Officer shall be a member of the Institutional Biosafety Committee.*¹⁵

BIO Comments:

BIO concurs with this change.

As noted above, BIO recommends that references to the IBC should specify “for the IBC that reviews and approves such research”, to provide clarity for institutions that have more than one IBC registered with NIH.

4. A new Section IV-B-3-c is added with the following text:

Section IV–B–3–c. The institution shall appoint a Biological Safety Officer if it engages in recombinant or synthetic nucleic acid molecule research that

¹⁴ Id.

¹⁵ 88 Fed. Reg. at 54339.



involves gene drive modified organisms. The Biological Safety Officer shall be a member of the Institutional Biosafety Committee.¹⁶

BIO Comments:

BIO concurs with this change. As noted above, BIO recommends that references to the IBC should specify “for the IBC that reviews and approves such research.”

VI. New language addressing potential ecosystem impacts

A new Section V-N is proposed as follows:

Determination of whether a gene drive modified organism has a potential for serious detrimental impact on managed (agricultural, forest, grassland) or natural ecosystems should be made by the Principal Investigator and the Institutional Biosafety Committee, in consultation with scientists knowledgeable of gene drive technology, the environment, and ecosystems in the geographic area of the research.¹⁷

BIO Comment:

BIO concurs with this new addition to the NIH Guidelines.

VII. New language addressing GDMOs and exempt organisms

Appendices C-III-A Exceptions and C-IV-A Exceptions are proposed to be amended by adding new GDMO text as follows:

and (v) experiments involving gene drive modified organisms (Section III-D-8).

BIO Comment:

BIO concurs with the addition of this new text to Appendices C-III-A and C-IV-A of the NIH Guidelines.

VIII. Replacing the term “Helper Virus” with “Helper System”

¹⁶ *Id.*

¹⁷ *Id.*



The term “helper virus” is proposed to be replaced in Sections III-D-3 and III-E-1 with the term “helper system”.

BIO Comments:

As a general matter, BIO concurs with this change. BIO suggests, however, that the General Definitions in the Guidelines should also be revised to include a definition of “helper systems” that is consistent with the explanation in the *Federal Register* notice that examples include “transient transfection systems, packaging cell lines, replicon systems, etc.”¹⁸ This would ensure that there is not the possibility of confusion as to what is meant by this term.

BIO appreciates the opportunity to provide public comments on the draft proposal to revise and update the NIH Guidelines. Please feel free to contact me directly if you have any questions about our comments.

Respectfully submitted,

A handwritten signature in black ink that reads "Leah Buchman".

Leah Buchman, Ph.D.
Regulatory Policy, Agriculture and Environment
Biotechnology Innovation Organization

¹⁸ 88 Fed. Reg. 54332, at 54340.

Submit date: 10/10/2023

I am responding to this RFI: On behalf of an organization

Name: LBNL Institutional Biosafety Committee

Name of Organization: Lawrence Berkeley National Lab

Type of Organization: Other

Type of Organization-Other: Federally funded research and development center

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

Please see attached file

2. Comment - NIH is seeking input on its proposals:

Please see attached file

Uploaded File:

Lawrence-Berkeley-National-Lab-Comments-for-NIH-Proposed-Updates.docx

Email: chips@lbl.gov

Comments for NIH Office of Science Policy

As committee members of the Institutional Biosafety Committee (IBC) who oversee the biosafety and biosecurity of U.S. government-funded research subject to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acids (NIH Guidelines)*, we are writing to provide our comments, questions, and concerns about the proposed updates to the NIH Guidelines described in the Federal Register, document number 2023-17178, citation 88 FR 54332. We appreciate this opportunity to comment on the August 2023 proposed NIH Guidelines updates from the NIH Office of Science Policy.

NIH Guidelines Proposal - GDMO: [\[excerpt from Comment Form\]](#)

Specific to the part of the proposal dealing with gene drive modified organisms. NIH proposed to:

- 1) clarify minimum containment requirements for research involving gene drive modified organisms
- 2) propose considerations for risk assessment
- 3) define additional institutional responsibilities regarding Institutional Biosafety Committees and Biosafety Officers

Lawrence Berkeley National Lab Comments:

The proposed addition of Gene Drive Modified Organisms (GDMO) into the NIH Guidelines does provide valuable guidance and instruction on institutional oversight and biosafety for research and reduced risk, however, some of the requirements restricts Institutional Biosafety Committee to conduct risk assessment and develop controls pertaining to the risk specific to each organism and research.

Our Institution has compiled comments, questions, and concerns on updates to specific sections:

- NIH Guidelines Section I-E:

Recommend adding the definition for a Gene Drive Modified Organism in Section I-E of the NIH Guidelines

- NIH Guidelines Section II-A-3:

In the risk assessment section of the proposed updates, what is considered biosafety data? Is it publications showing attenuated gene drives or safety data on the specific selected gene drive? Recommend adding guidance on what to do when publications is not available. Can the institution perform pilot work to demonstrate safety?

- NIH Guidelines Section III-D-8:

Some organisms and life stages of organisms would have greatly reduced risk of accidental release into the environment. Setting a minimum BSL reduces an institutions ability to perform a risk assessment based on the research, facility containment, etc. and determine an appropriate biosafety level. The broad range of possible targets for the creation of GDMO do not all warrant immediate assignment at BSL-2/N/P/AC.

Gene drive technology is advancing toward a more managed and control approach, improving safety and reducing risk to the environment. There are gene drives used to create GDMO where the drive is silenced or spliced out in future offspring or requires an unnatural mechanism to engage the gene of interest. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism and when the offspring would no longer meet the definition of GDMO. Clarification from the NIH on what is a GDMO is necessary as gene drive technology advances.

Will there be a process for downgrade requests to the NIH Office of Science Policy? A request for downgrade is described under Section III-D-4. Recommend adding this option to Section III-D-8.

- NIH Guidelines III-E-3:

Would this require that all offspring from GDMO be handled at ABSL-2? There are gene drives used to create transgenic mice where the drive is silenced or spliced out in future offspring. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism. Clarification from the NIH on what is a GDMO is necessary.

Recommend updating the FAQs for Research on Genetically Modified (Transgenic) Animals.

- NIH Guidelines IV-B-2-a-(1):

There are limited "Gene Drive" experts in the field and often at smaller institutions the 1 expert is the 1 PI submitting a gene drive BUA. Can the NIH provide clarity on Ad Hoc reviewers for an IBC?

NIH Guidelines Section V-N:

Can the NIH provide clarity on Ad Hoc reviewers for an IBC? Many institutions will need to use an Ad Hoc. Does an Ad Hoc reviewer need to be local? What are the anticipated qualifications to be an Ad Hoc Reviewer?

When describing managed or natural ecosystems, this wording would be better addressed by discussing impact to local environment and ecosystems in cases of accidental release.

- NIH Guidelines Section III-F-8 Appendix C-III-A:

This section will now require NIH exempt work with *Saccharomyces* and gene drive to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt at BSL-1 to now require IBC approval prior to start of work at BSL-2. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and BSL-1 when used as a gene drive modified organism?

- NIH Guidelines Section III-F-8 Appendix C-IV-A:

This section will now require NIH exempt work with *Saccharomyces* and gene drive to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt at BSL-1 to now require IBC approval prior to start of work at BSL-2. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and BSL-1 when used as a gene drive modified organism?

NIH Guidelines Proposal – Helper virus: [\[excerpt from Comment Form\]](#)

In addition, NIH is seeking input on its proposal to:

1. replace the term “helper viruses” with the broader term “helper systems.”; and
2. reclassify West Nile Virus (WNV) and Saint Louis Encephalitis Virus (SLEV) as risk group 2 agents for consistency with containment guidance provided in *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*, 6th edition.

Lawrence Berkeley National Lab Comments:

- NIH Guidelines Section: III-D-3 and III-E-1

Can a definition of helper system be added into definitions Section of the NIH Guidelines? The Federal Register justification provided examples like “helper systems (*e.g.*, transient transfection systems, packaging cell lines, replicon systems, etc.)”. This will aid institutions in ensuring the helper system is evaluated appropriately under this section of the NIH Guidelines.

We thank you for your consideration of these comments, questions, and concerns.

Respectfully submitted,

Lawrence Berkeley National Lab IBC

Submit date: 10/10/2023

I am responding to this RFI: On behalf of an organization

Name: Thomas Leach

Name of Organization: New Jersey Association for Biomedical Research

Type of Organization: Professional org association

Role: Member of the public

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

On behalf of the members of the New Jersey Association for Biomedical Research (NJABR), whose members include the nation's leading life sciences companies and research universities, thank you for the opportunity to comment on the proposal to revise the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) to include specific considerations and requirements for conducting research involving gene drive modified organisms (GDMO) in contained research settings.

NJABR has a concern regarding the proposed changes to the NIH Guidelines in Section III-E-3 3 (Experiments Involving Transgenic Rodents). Specifically, the words "or use" are included in the first sentence in this subsection and is proposed to read as follows: "This section covers 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)." In particular, NJABR is concerned that the inclusion of the words "or use" in the NIH Guidelines will add significant, unnecessary administrative and practical burdens to researchers and institutional administrative and compliance staff. This contradicts directives in the 21st Century Cures Act, and we urge NIH to reconsider the need for the inclusion of the words "or use" in this section.

NJABR recognizes that the addition of "or use" in Section III-E-3 3 can also be utilized to qualify that Section III-E-3 3 is intended to cover the generation and subsequent use of an in-house generated transgenic rodents. If this is NIH's intent, we respectfully ask that additional language be added to make this more clear to ensure the language is not unnecessarily interpreted.

Thank you for reviewing our brief comments on this matter. If you have any questions, please do not hesitate to contact me.

Sincerely,

Thomas A. Leach

Executive Director

2. Comment - NIH is seeking input on its proposals:

Email: leach@njabr.org

Submit date: 10/10/2023

I am responding to this RFI: On behalf of myself

Name: Adrienne E. Zweifel

Name of Organization: University of California

Type of Organization: University

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

The proposed addition of Gene Drive Modified Organisms (GDMO) into the NIH Guidelines provides guidance and instruction on institutional oversight and biosafety for research with an emergency technology that has a complex risk profile. Updates include specific requirements or expectations placed on the researcher, biosafety officer, IBC, and institution. Some of these expectations add complexity to the oversight mechanism, reduce the IBC's ability to conduct risk assessment based biosafety level determinations, and create more questions on how to appropriately implement the NIH Guidelines.

- NIH Guidelines, Section I-E-7 – The definition of "gene drive" states, "a particular heritable element biases inheritance in its favor..." implies that the organisms have alleles for certain genes involved. Does the definition of "gene drive" exclude prokaryotes?

- NIH Guidelines, Section II-A-3:

The text, "The appropriate containment level may be equivalent to the Risk Group classification of the agent, or it may be raised or lowered as a result of the above considerations" seems to contradict the latter statement about minimum containment level as BL2. I acknowledge that this text is not new but the proposed changes to this section is in this context. It can be confusing if GDMO is read in this context.

In the risk assessment section of the proposed updates, what is considered biosafety data? Is it publications showing attenuated gene drives or safety data on the specific selected gene drive? Publications may not be available and institutions may want pilot projects to be performed by the researcher to provide biosafety data. Recommend inclusion of guidance for pilot projects that would provide biosafety data.

- NIH Guidelines, Section II-A-3-3 – The reference to "more stringent containment measures" is vague. Do local IBCs have leeway to determine what "more stringent" means, or is there an acceptable definition for that term?

- NIH Guidelines, Sections IIID and IIIE – There are some gene drives that are used where the drive is silenced or spliced out in future offspring (whether animals or plants), please comment to verify that this "feature" takes these organisms outside of the definition of GDMO.

- NIH Guidelines, Section III-D-8:

Some organisms and life stages of organisms would have greatly reduced risk of accidental release into the environment. Setting a minimum BSL reduces an institution's ability to perform a risk assessment

based on the research, facility containment, etc. and determine an appropriate biosafety level. The broad range of possible targets for the creation of GDMO do not all warrant immediate assignment at BSL-2/N/P/AC.

Gene drive technology is advancing toward a more managed and control approach, improving safety and reducing risk to the environment. There are gene drives used to create GDMO where the drive is silenced or spliced out in future offspring or requires an unnatural mechanism to engage the gene of interest. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism and when the offspring would no longer meet the definition of GDMO. Clarification from the NIH on what is a GDMO is necessary as gene drive technology advances.

Will there be a process for downgrade requests to the NIH Office of Science Policy? A request for downgrade is described under Section III-D-4. Recommend adding this option to Section III-D-8.

- NIH Guidelines III-E-3:

Would this require that all offspring from GDMO be handled at ABSL-2? There are gene drives used to create transgenic mice where the drive is silenced or spliced out in future offspring. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism. Clarification from the NIH on what is a GDMO is necessary.

Recommend updating the FAQs for Research on Genetically Modified (Transgenic) Animals.

- NIH Guidelines, Section IV-B-2-a-(1):

There are limited “Gene Drive” experts in the field and often at smaller institutions the lone expert is the single PI submitting a gene drive BUA. Can the NIH provide clarity on Ad Hoc reviewers for an IBC? Does an Ad Hoc reviewer need to be local? What are the anticipated qualifications to be an Ad Hoc Reviewer?

- NIH Guidelines, Section V-N:

Can the NIH provide clarity on Ad Hoc reviewers for an IBC? Many institutions will need to use an Ad Hoc. Does an Ad Hoc reviewer need to be local? What are the anticipated qualifications to be an Ad Hoc Reviewer?

When describing managed or natural ecosystems, this wording would be better addressed by discussing impact to local environment and ecosystems in cases of accidental release.

- NIH Guidelines Section III, F-8 Appendix C-III-A:

This section will now require NIH exempt work with *Saccharomyces* and gene drive to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt at BSL-1 to now require IBC approval prior to start of work at BSL-2. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and BSL-1 when used as a gene drive modified organism?

- NIH Guidelines Section III-F-8 Appendix C-IV-A:

This section will now require NIH exempt work with *Saccharomyces* and gene drive to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt at BSL-1 to now require IBC approval prior to start of work at BSL-2. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and BSL-1 when used as a gene drive modified organism?

If implemented, the proposed updates to the NIH Guidelines would impede vital research efforts. Given the stringent biosafety regulations and thorough risk assessment by the IBCs, requiring a specific Biosafety Level for containment of GDMO, without a process for lowering the BSL based on risk, limits the ability of the IBC to operate as designed, and would also raise research costs and impede the cost-effectiveness of NIH-sponsored research.

IBC's are aware of limitations to subject matter expertise in the field of gene drive. Additional clarity and guidance on selection of Ad Hoc reviewers will support institutions to supplement expertise when necessary. It is highly encouraged that the NIH OSP consider equity and access to Ad Hoc subject matter expertise for institutions of all sizes and research profiles.

2. Comment - NIH is seeking input on its proposals:

- NIH Guidelines, Section: III-D-3 and III-E-1

Can a definition of helper system be added into definitions Section of the NIH Guidelines? The Federal Register justification provided examples like "helper systems (e.g., transient transfection systems, packaging cell lines, replicon systems, etc.)". This will aid institutions in ensuring the helper system is evaluated appropriately under this section of the NIH Guidelines.

Email: azweifel@ucdavis.edu

Submit date: 10/10/2023

I am responding to this RFI: On behalf of an organization

Name: Thomas Leach

Name of Organization: Pennsylvania Society for Biomedical Research

Type of Organization: Professional org association

Role: Member of the public

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

On behalf of the members of the Pennsylvania Society for Biomedical Research (PSBR), whose members include the nation's leading life sciences companies and research universities, thank you for the opportunity to comment on the proposal to revise the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) to include specific considerations and requirements for conducting research involving gene drive modified organisms (GDMO) in contained research settings.

PSBR has a concern regarding the proposed changes to the NIH Guidelines in Section III-E-3 3 (Experiments Involving Transgenic Rodents). Specifically, the words "or use" are included in the first sentence in this subsection and is proposed to read as follows: "This section covers 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)." In particular, PSBR is concerned that the inclusion of the words "or use" in the NIH Guidelines will add significant, unnecessary administrative and practical burdens to researchers and institutional administrative and compliance staff. This contradicts directives in the 21st Century Cures Act, and we urge NIH to reconsider the need for the inclusion of the words "or use" in this section.

PSBR recognizes that the addition of "or use" in Section III-E-3 3 can also be utilized to qualify that Section III-E-3 3 is intended to cover the generation and subsequent use of an in-house generated transgenic rodents. If this is NIH's intent, we respectfully ask that additional language be added to make this more clear to ensure the language is not unnecessarily interpreted.

Thank you for reviewing our brief comments on this matter. If you have any questions, please do not hesitate to contact me.

Sincerely,

Thomas A. Leach

Executive Director

2. Comment - NIH is seeking input on its proposals:

Email: tom@psbr.org

Submit date: 10/10/2023

I am responding to this RFI: On behalf of an organization

Name: Vanessa Cook

Name of Organization: UC Merced

Type of Organization: University

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

The proposed addition of Gene Drive Modified Organisms (GDMO) into the NIH Guidelines provides guidance and instruction on institutional oversight and biosafety for research with an emergency technology that has a complex risk profile. Updates include specific requirements or expectations placed on the researcher, biosafety officer, IBC, and institution. Some of these expectations add complexity to the oversight mechanism, reduce the IBC's ability to conduct risk assessment based biosafety level determinations, and create more questions on how to appropriately implement the NIH Guidelines.

The IBC has compiled comments, questions, and concerns on updates to specific sections:

NIH Guidelines Section I-E:

Recommend adding the definition for a Gene Drive Modified Organism in Section I-E of the NIH Guidelines

NIH Guidelines Section II-A-3:

In the risk assessment section of the proposed updates, what is considered biosafety data? Is it publications showing attenuated gene drives or safety data on the specific selected gene drive? Publications may not be available and institutions may want pilot projects to be performed by the researcher to provide biosafety data. Recommend inclusion of guidance for pilot projects that would provide biosafety data.

NIH Guidelines Section III-D-8:

Some organisms and life stages of organisms would have greatly reduced risk of accidental release into the environment (e.g., zebrafish). Setting a minimum BSL for all gene drive organisms reduces an institutions ability to perform a risk assessment based on the research, facility containment, etc. and determine an appropriate biosafety level. The broad range of possible targets for the creation of GDMO do not all warrant immediate assignment at BSL-2/N/P/AC.

Gene drive technology is advancing toward a more managed and controlled approach, improving safety and reducing risk to the environment. There are gene drives used to create GDMO where the drive is silenced or spliced out in future offspring or requires an unnatural mechanism to engage the gene of interest. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism and when the offspring would no longer meet the definition of GDMO. Clarification from the NIH on what is a GDMO is necessary as gene drive technology advances.

Will there be a process for downgrade requests to the NIH Office of Science Policy? A request for downgrade is described under Section III-D-4. Recommend adding this option to Section III-D-8.

NIH Guidelines III-E-3:

Would this require that all offspring from GDMO be handled at ABSL-2? There are gene drives used to create transgenic mice where the drive is silenced or spliced out in future offspring. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism. Clarification from the NIH on what is a GDMO is necessary.

Recommend updating the FAQs for Research on Genetically Modified (Transgenic) Animals.

NIH Guidelines IV-B-2-a-(1):

There are limited “Gene Drive” experts in the field and often at smaller institutions the only expert is the PI submitting a gene drive Biohazard Use Authorization (BUA). Can the NIH provide clarity on Ad Hoc reviewers of protocols involving gene drive for an IBC? Does an Ad Hoc reviewer need to be local? What are the anticipated qualifications to be an Ad Hoc reviewer? Do Ad Hoc reviewers serve solely as subject matter experts or are they voting members on gene drive protocols?

NIH Guidelines Section V-N:

Can the NIH provide clarity on Ad Hoc reviewers for an IBC? Many institutions will need to use an Ad Hoc. Does an Ad Hoc reviewer need to be local? What are the anticipated qualifications to be an Ad Hoc Reviewer? Do Ad Hoc reviewers serve solely as subject matter experts or are they voting members on gene drive protocols?

When describing managed or natural ecosystems, this wording would be better addressed by discussing impact to local environment and ecosystems in cases of accidental release.

NIH Guidelines Section III-F-8 Appendix C-III-A:

This section would now require NIH exempt work with gene drive in *Saccharomyces cerevisiae* to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt and appropriate to be handled at BSL-1 to now require IBC approval prior to start of work at BSL-2 containment. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and handled at BSL-1 when used as a gene drive modified organism?

NIH Guidelines Section III-F-8 Appendix C-IV-A:

This section would now require NIH exempt work with gene drive in *Saccharomyces cerevisiae* to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt and appropriate to be handled at BSL-1 to now require IBC approval prior to start of work at BSL-2 containment. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and handled at BSL-1 when used as a gene drive modified organism?

If implemented, the proposed updates to the NIH Guidelines would impede vital research efforts. Given the stringent biosafety regulations and thorough risk assessment by the individual university IBCs, requiring a specific Biosafety Level for containment of GDMO, without a process for lowering the BSL based on risk, limits the ability of the IBC to operate as designed, and would also raise research costs and impede the cost-effectiveness of NIH-sponsored research.

IBCs are aware of limitations to subject matter expertise in the field of gene drive. Additional clarity and guidance on selection of Ad Hoc reviewers will support institutions to supplement expertise when necessary. It is highly encouraged that the NIH OSP consider equity and access to Ad Hoc subject matter expertise for institutions of all sizes and research profiles.

2. Comment - NIH is seeking input on its proposals:

Request addition of definition of “helper system” into the definitions section of the NIH Guidelines. The Federal Register justification provided examples like “helper systems (e.g., transient transfection systems, packaging cell lines, replicon systems, etc.)”. This will aid institutions in ensuring the helper system is evaluated appropriately under this section of the NIH Guidelines.

Email: vcook@ucmerced.edu

Submit date: 10/10/2023

I am responding to this RFI: On behalf of an organization

Name: James Baugh

Name of Organization: University of California Berkeley

Type of Organization: University

Role: Member of the public

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

The proposed addition of Gene Drive Modified Organisms (GDMO) into the NIH Guidelines provides guidance and instruction on institutional oversight and biosafety for research with an emergency technology that has a complex risk profile. Updates include specific requirements or expectations placed on the researcher, biosafety officer, IBC, and institution. Some of these expectations add complexity to the oversight mechanism, reduce the IBC's ability to conduct risk assessment based biosafety level determinations, and create more questions on how to appropriately implement the NIH Guidelines.

The IBC has compiled comments, questions, and concerns on updates to specific sections:

- NIH Guidelines Section I-E:

Recommend adding the definition for a Gene Drive Modified Organism in Section I-E of the NIH Guidelines

- NIH Guidelines Section II-A-3:

In the risk assessment section of the proposed updates, what is considered biosafety data? Is it publications showing attenuated gene drives or safety data on the specific selected gene drive? Publications may not be available and institutions may want pilot projects to be performed by the researcher to provide biosafety data. Recommend inclusion of guidance for pilot projects that would provide biosafety data.

- NIH Guidelines Section III-D-8:

Some organisms and life stages of organisms would have greatly reduced risk of accidental release into the environment. Setting a minimum BSL reduces an institutions ability to perform a risk assessment based on the research, facility containment, etc. and determine an appropriate biosafety level. The broad range of possible targets for the creation of GDMO do not all warrant immediate assignment at BSL-2/N/P/AC.

Gene drive technology is advancing toward a more managed and control approach, improving safety and reducing risk to the environment. There are gene drives used to create GDMO where the drive is silenced or spliced out in future offspring or requires an unnatural mechanism to engage the gene of interest. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism and when the offspring would no longer meet the definition of GDMO. Clarification from the NIH on what is a GDMO is necessary as gene drive technology advances.

Will there be a process for downgrade requests to the NIH Office of Science Policy? A request for downgrade is described under Section III-D-4. Recommend adding this option to Section III-D-8.

- NIH Guidelines III-E-3:

Would this require that all offspring from GDMO be handled at ABSL-2? There are gene drives used to create transgenic mice where the drive is silenced or spliced out in future offspring. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism. Clarification from the NIH on what is a GDMO is necessary.

Recommend updating the FAQs for Research on Genetically Modified (Transgenic) Animals.

- NIH Guidelines IV-B-2-a-(1):

There are limited “Gene Drive” experts in the field and often at smaller institutions the 1 expert is the 1 PI submitting a gene drive BUA. Can the NIH provide clarity on Ad Hoc reviewers for an IBC? Does an Ad Hoc reviewer need to be local? What are the anticipated qualifications to be an Ad Hoc Reviewer?

- NIH Guidelines Section V-N:

Can the NIH provide clarity on Ad Hoc reviewers for an IBC? Many institutions will need to use an Ad Hoc. Does an Ad Hoc reviewer need to be local? What are the anticipated qualifications to be an Ad Hoc Reviewer?

When describing managed or natural ecosystems, this wording would be better addressed by discussing impact to local environment and ecosystems in cases of accidental release.

- NIH Guidelines Section III-F-8 Appendix C-III-A:

This section will now require NIH exempt work with *Saccharomyces* and gene drive to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt at BSL-1 to now require IBC approval prior to start of work at BSL-2. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and BSL-1 when used as a gene drive modified organism?

- NIH Guidelines Section III-F-8 Appendix C-IV-A:

This section will now require NIH exempt work with *Saccharomyces* and gene drive to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt at BSL-1 to now require IBC approval prior to start of work at BSL-2. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and BSL-1 when used as a gene drive modified organism?

If implemented, the proposed updates to the NIH Guidelines would impede vital research efforts. Given the stringent biosafety regulations and thorough risk assessment by the IBCs, requiring a specific Biosafety Level for containment of GDMO, without a process for lowering the BSL based on risk, limits the ability of the IBC to operate as designed, and would also raise research costs and impede the cost-effectiveness of NIH-sponsored research.

IBC's are aware of limitations to subject matter expertise in the field of gene drive. Additional clarity and guidance on selection of Ad Hoc reviewers will support institutions to supplement expertise when necessary. It is highly encouraged that the NIH OSP consider equity and access to Ad Hoc subject matter expertise for institutions of all sizes and research profiles.

2. Comment - NIH is seeking input on its proposals:

- NIH Guidelines Section: III-D-3 and III-E-1

Can a definition of helper system be added into definitions Section of the NIH Guidelines? The Federal Register justification provided examples like "helper systems (e.g., transient transfection systems, packaging cell lines, replicon systems, etc.)". This will aid institutions in ensuring the helper system is evaluated appropriately under this section of the NIH Guidelines.

Uploaded File:

UCB-Comments-for-NIH-Proposed-Updates.docx

Email: jimbaugh@berkeley.edu

Comments for NIH Office of Science Policy

As a member of the University of California system, we are writing to provide comments, questions, and concerns about the proposed updates to the NIH Guidelines described in the Federal Register, document number 2023-17178, citation 88 FR 54332. We appreciate this opportunity to comment on the August 2023 proposed NIH Guidelines updates from the NIH Office of Science Policy.

NIH Guidelines Proposal - GDMO: [\[excerpt from Comment Form\]](#)

Specific to the part of the proposal dealing with gene drive modified organisms. NIH proposed to:

- 1) clarify minimum containment requirements for research involving gene drive modified organisms
- 2) propose considerations for risk assessment
- 3) define additional institutional responsibilities regarding Institutional Biosafety Committees and Biosafety Officers

Comments:

The proposed addition of Gene Drive Modified Organisms (GDMO) into the NIH Guidelines provides guidance and instruction on institutional oversight and biosafety for research with an emergency technology that has a complex risk profile. Updates include specific requirements or expectations placed on the researcher, biosafety officer, IBC, and institution. Some of these expectations add complexity to the oversight mechanism, reduce the IBC's ability to conduct risk assessment based biosafety level determinations, and create more questions on how to appropriately implement the *NIH Guidelines*.

The IBC has compiled comments, questions, and concerns on updates to specific sections:

- NIH Guidelines Section I-E:

Recommend adding the definition for a Gene Drive Modified Organism in Section I-E of the NIH Guidelines

- NIH Guidelines Section II-A-3:

In the risk assessment section of the proposed updates, what is considered biosafety data? Is it publications showing attenuated gene drives or safety data on the specific selected gene drive? Publications may not be available and institutions may want pilot projects to be performed by the researcher to provide biosafety data. Recommend inclusion of guidance for pilot projects that would provide biosafety data.

- NIH Guidelines Section III-D-8:

Some organisms and life stages of organisms would have greatly reduced risk of accidental release into the environment. Setting a minimum BSL reduces an institutions ability to perform a risk assessment based on the research, facility containment, etc. and determine an appropriate biosafety level. The broad range of possible targets for the creation of GDMO do not all warrant immediate assignment at BSL-2/N/P/AC.

Gene drive technology is advancing toward a more managed and control approach, improving safety and reducing risk to the environment. There are gene drives used to create GDMO where the drive is silenced or spliced out in future offspring or requires an unnatural mechanism to engage the gene of interest. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism and when the offspring would no longer meet the definition of GDMO. Clarification from the NIH on what is a GDMO is necessary as gene drive technology advances.

Will there be a process for downgrade requests to the NIH Office of Science Policy? A request for downgrade is described under Section III-D-4. Recommend adding this option to Section III-D-8.

- NIH Guidelines III-E-3:

Would this require that all offspring from GDMO be handled at ABSL-2? There are gene drives used to create transgenic mice where the drive is silenced or spliced out in future offspring. It should be up to the Principle Investigator and Institutional Biosafety Committee to perform a risk assessment and determine when an organism is considered a Gene Drive Modified Organism. Clarification from the NIH on what is a GDMO is necessary.

Recommend updating the FAQs for Research on Genetically Modified (Transgenic) Animals.

- NIH Guidelines IV-B-2-a-(1):

There are limited "Gene Drive" experts in the field and often at smaller institutions the 1 expert is the 1 PI submitting a gene drive BUA. Can the NIH provide clarity on Ad Hoc

reviewers for an IBC? Does an Ad Hoc reviewer need to be local? What are the anticipated qualifications to be an Ad Hoc Reviewer?

- NIH Guidelines Section V-N:

Can the NIH provide clarity on Ad Hoc reviewers for an IBC? Many institutions will need to use an Ad Hoc. Does an Ad Hoc reviewer need to be local? What are the anticipated qualifications to be an Ad Hoc Reviewer?

When describing managed or natural ecosystems, this wording would be better addressed by discussing impact to local environment and ecosystems in cases of accidental release.

- NIH Guidelines Section III-F-8 Appendix C-III-A:

This section will now require NIH exempt work with *Saccharomyces* and gene drive to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt at BSL-1 to now require IBC approval prior to start of work at BSL-2. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and BSL-1 when used as a gene drive modified organism?

- NIH Guidelines Section III-F-8 Appendix C-IV-A:

This section will now require NIH exempt work with *Saccharomyces* and gene drive to be covered under III-D and reviewed and approved by the IBC prior to start of work. This is an undue burden for an agent that was previously exempt at BSL-1 to now require IBC approval prior to start of work at BSL-2. Would the NIH consider the agents listed under III-F-8 Appendix C as possibly being under III-E and BSL-1 when used as a gene drive modified organism?

If implemented, the proposed updates to the *NIH Guidelines* would impede vital research efforts. Given the stringent biosafety regulations and thorough risk assessment by the IBCs, requiring a specific Biosafety Level for containment of GDMO, without a process for lowering the BSL based on risk, limits the ability of the IBC to operate as designed, and would also raise research costs and impede the cost-effectiveness of NIH-sponsored research.

IBC's are aware of limitations to subject matter expertise in the field of gene drive. Additional clarity and guidance on selection of Ad Hoc reviewers will support institutions to supplement expertise when necessary. It is highly encouraged that the NIH OSP consider equity and access to Ad Hoc subject matter expertise for institutions of all sizes and research profiles.

NIH Guidelines Proposal – Helper virus: [\[excerpt from Comment Form\]](#)

In addition, NIH is seeking input on its proposal to:

1. replace the term “helper viruses” with the broader term “helper systems.”; and
2. reclassify West Nile Virus (WNV) and Saint Louis Encephalitis Virus (SLEV) as risk group 2 agents for consistency with containment guidance provided in *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*, 6th edition.

Comments:

- NIH Guidelines Section: III-D-3 and III-E-1

Can a definition of helper system be added into definitions Section of the NIH Guidelines? The Federal Register justification provided examples like “helper systems (e.g., transient transfection systems, packaging cell lines, replicon systems, etc.)”. This will aid institutions in ensuring the helper system is evaluated appropriately under this section of the NIH Guidelines.

We thank you for your consideration of these comments, questions, and concerns!

Respectfully submitted,

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Submit date: 10/10/2023

I am responding to this RFI: On behalf of an organization

Name: Eve Granatosky

Name of Organization: American Society of Plant Biologists (ASPB)

Type of Organization: Professional org association

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

The American Society of Plant Biologists (ASPB), founded in 1924 as the American Society of Plant Physiologists, was established to promote the growth and development of plant biology, to encourage and publish research in plant biology, and to promote the interests and professional advancement of plant scientists in general. ASPB members conduct research to enhance understanding of plant biology and, among other applications, its impacts on public health and wellbeing. We welcome the opportunity to provide perspective from the plant biology research community on this important policy topic that impacts a range of biologists from many disciplines.

(3) ASPB is concerned with the proposed requirement for a Biosafety Officer (BSO) given any research involving gene drives. This requirement is in the amendment to Section IV-B-1-c and Section IV-B-3c. The original IV-B-1-c only requires a BSO if there is work at BSL3 or BSL4, or if it is performed on a large scale, and ASPB finds this requirement reasonable. However, considering NIH proposes that the minimum requirement for gene drive research would warrant BSL2, this additional requirement of a BSO would be unnecessarily onerous for research already conducted under BSL2 conditions.

ASPB agrees with NIH's proposal outlined in Section IV-B-2-a-(1) to require an institution conducting gene drive research have an Institutional Biosafety Committee with adequate expertise, but NIH's current language includes only human subject research. ASPB suggests this section be amended to delete mention of specific types of research and instead propose, for example, that "the institution must ensure that the Institutional Biosafety Committee has adequate expertise to assess the research projects for which it is responsible, using ad hoc consultants if necessary."

Thank you for the opportunity to comment, and please let us know if ASPB can provide additional assistance on this topic.

2. Comment - NIH is seeking input on its proposals:

n/a

Email: eve@lewis-burke.com

Submit date: 10/10/2023

I am responding to this RFI: On behalf of an organization

Name: Ryan Lisk

Name of Organization: The University of Texas Southwestern Medical Center

Type of Organization: University

Role: Institutional official

1. Comment specific to the part of the proposal dealing with gene drive modified organisms:

We request clarification on whether the proposed minimum containment for Gene Drive Modified Organisms (GDMOs) at biosafety level 2 (BSL-2) is expected to be enforced retroactively. This may include reevaluation and/or reclassification of current work practices already in place with potential procedural changes for researchers. With respect to administrative impacts, the reclassification would likely place a strain on current Institutional Biosafety Committee (IBC) processes leading to extended review times and approvals. The potential fiscal implications remain unclear but may include hiring of additional staff to review research projects that qualify for the revised scope.

The proposed minimum containment for GDMOs at animal biosafety level 2 (ABSL-2) potentially has both fiscal and administrative impacts. Current processes place certain types of gene drive work (such as CRISPR) under biosafety level 1 (BSL-1) housing, to include work in both whole animals and arthropods. Movement of this work to BSL-2 containment for housing areas may require facility modification such as directional airflow, one-pass air, and potential retrofits of certain spaces to include biosafety cabinets (BSCs). Additionally, renovation of these spaces will increase expenditures that are currently not budgeted for. Administratively, the proposed changes have an impact on the scope of current institutional policies and SOPs and will require a significant amount of time to make implement those changes accordingly.

2. Comment - NIH is seeking input on its proposals:

Email: Ryan.Lisk@UTSouthwestern.edu

