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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.

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[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.

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[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

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[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 <u>ad hoc</u> 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"

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[16] *Id.*

[17] *Id.*

The term "helper virus" is proposed to be replace 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,

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[18] 88 Fed. Reg. 54332, at 54340.