

**ABSA**

American Biological Safety Association

1200 Allanson Road • Mundelein, IL 60060-3808 • 866-425-1385 • 847-949-1517
Fax: 847-566-4580 • E-mail: absa@absa.org • Web Site: www.absa.org**President**

Robert P. Ellis, PhD, CBSP
Colorado State University
Environmental Health Services
Campus Mail Stop 6021
Fort Collins, CO 80523-6021
970-491-6729
Fax: 970-491-4804
robert.ellis@colostate.edu

President-Elect

Benjamin A. Fontes, MPH, CBSP
Yale University
Office of EH&S, 1st Floor
135 College Street
New Haven, CT 06510
203-737-5009
Fax: 203-785-7588
benjamin.fontes@yale.edu

Secretary

Paul J. Meechan, PhD, RBP, CBSP
Merck Research Laboratories
WP44-204, P.O. Box 4
West Point, PA 19486-0004
215-652-0744
Fax: 215-993-0738
paul_meechan@merck.com

Treasurer

Leslie Delpin, MS, RBP, CBSP
University of Connecticut
3102 Horsebarn Hill Road, Unit 4097
Storrs, CT 06269-4097
860-486-2436
Fax: 860-486-1106
lm.delpin@uconn.edu

Past-President

Christina Z. Thompson, MS, RBP, CBSP
Thompson Biosafety, LLC
2410 Wayne Drive
Greenfield, IN 46140
317-326-8352
Fax: 317-326-8352
cztoneputt@aol.com

Councilors

LouAnn Burnett, MS, CBSP (10)
Joseph Kanabrocki, PhD, CBSP (09)
Barbara Fox Nellis, RBP, CBSP (11)
Janet Peterson, RBP, CBSP (09)

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Edward John Stygar, III, MBA
ed@absaoffice.org

Dr. Jaqueline Corrigan-Curray**Office of Biotechnology Activities****National Institutes of Health****6705 Rockledge Drive****Suite 750 MSC 7985****Bethesda, MD 20892-7985****May 28, 2009****Dear Dr. Corrigan-Curray,**

The American Biological Safety Association (ABSA) is an international group of biological safety professionals which is known as one of the world's foremost resources on biological safety practices. We have reviewed the proposed revisions to the "NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)" which were announced in the Federal Register on March 4, 2009. Please consider the comments that follow regarding this proposal.

General Comments

The addition of Institutional Biosafety Committee (IBC) reviews of experiments involving synthetic nucleic acids will require additional expertise on the local IBCs. The NIH Guidelines should reflect the need for additional expertise on the local IBCs if these reviews are to have the intended scope and benefit. The Recombinant DNA Advisory Committee (RAC) will likely face similar challenges in its national reviews.

Specific Comments

Proposed Changes to Section I-A, Section I-B: The NIH Guidelines must be reviewed carefully and thoroughly for meaning when replacing the term "recombinant DNA molecules" with "recombinant and synthetic nucleic acid molecules." Section I-A states, "In accordance with this change in the scope of the NIH Guidelines, the term, 'recombinant DNA molecules' will be replaced with 'recombinant and synthetic nucleic acid molecules.'" To be clear, the replacement text should be 'recombinant and/or synthetic nucleic acid molecules.'" Consistent use of this distinction throughout the Guidelines should help to avoid possible confusion amongst the entities seeking to implement provisions of the NIH Guidelines. An alternative would be to use the single term, "nucleic acid" or "nucleic acids" instead of "recombinant and synthetic nucleic acid molecules" with a definition for "nucleic acid" or "nucleic acids" that makes the needed clarification.

Proposed Changes to Section I-B: Under “Definition”, the proposed text states: In the context of the NIH Guidelines, recombinant and synthetic nucleic acids are defined as: (i) Recombinant nucleic acid molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell, (ii) synthetic nucleic acid molecules that are chemically, or by other means, synthesized or amplified nucleic acid molecules that may wholly or partially contain functional equivalents of nucleotides, or (iii) molecules that result from the replication of those described in (i) or (ii) above.” The phrases used in this section do not provide the clarity required to make the clear distinctions needed to effectively apply the Guidelines to research. We suggest the following alternative text:

Section I-B-a. Definition. “In the context of the NIH Guidelines DNA, RNA and synthetic nucleic acids are considered to be nucleic acids regardless of their origin.”, or

Section I-B-a. Definition. “In the context of the NIH Guidelines recombinant nucleic acids (NA) are defined as molecules constructed by joining nucleic acid segments, regardless of their origin, into biochemically unique constructed molecules that can (i) replicate in a living cell or (ii) generate molecules that can replicate in a living cell.”

Proposed Changes to Section 1-B: The terms “low risk” and “high risk” need further characterization as applied to synthetic, nucleic acids. Possible means by which this characterization could be accomplished would be for NIH/OBA to develop and share “Fact Sheets” regarding low-risk and high-risk experiments. These “Fact Sheets” could better define these types of experiments and provide illustrative examples of each type of experiment. Inclusion of a decision tree detailing the process that should be considered when making these distinctions would contribute additional utility of these documents.

There is another need for such “Fact Sheets.” The announced scope of the revised NIH Guidelines would be inclusive of work of principal investigators (PIs) such as chemistry or engineering researchers. These PIs likely have no previous experience in conducting research that is considerate of the NIH Guidelines, and many of them may have no experience in risk assessments that are inherent to research considerate of these Guidelines. The language in any “Fact Sheets” should be in “lay language” to facilitate the understanding of these PIs regarding the NIH Guidelines. These fact sheets could also be helpful for IBC members who represent the entity’s community.

Proposed Changes to Section II-A-3: The following new paragraphs are proposed by NIH to be added to the Guidelines:

“[New Paragraph] While the initial risk assessment is based on the identification of the Risk Group of the parent agent, as technology moves forward, it may be possible to develop a chimera in which the parent agent may not be obvious. In such cases, the risk assessment should involve at least two levels of analysis. The first involves a consideration of the Risk Groups of the source(s) of the sequences and the second an analysis of the functional attributes of these sequences (e.g., sequence associated with

virulence factors, pathogenicity, transmissibility, etc.). It may be prudent to first consider the highest risk group classification of any agent sequence included in the chimera. Other factors to be considered include the percentage of the genome contributed by each of multiple parent agents, and the predicted function or intended purpose of each contributing sequence. The initial assumption should be that all sequences will function as predicted in the original host context.

The IBC must also be cognizant that the combination of certain sequences may result in an organism whose risk profile could be higher than that of the contributing organisms or sequences. The synergistic function of these sequences may be one of the key attributes to consider in deciding whether a higher containment level is warranted. A new biosafety risk may occur with a chimera formed through combination of sequences from a number of organisms or due to the synergistic effect of combining transgenes that results in a new phenotype.

These paragraphs reference the terms, “chimera” and “parent agent”. These terms are used for the first time in the Guidelines in these paragraphs. These terms do not have universal meaning between investigators, and the definition inconsistencies could result in differences in the application by investigators of these new provisions of the Guidelines. “Parent strain” is used frequently in the Guidelines, and it is widely and consistently recognized as being the wild-type origin from which a genetically modified organism is generated. It is proposed that the term “parent strain” be replaced with “parent agent.” Chimera could be defined as: “resulting nucleic acid derived from two or more genotypically diverse parent agent nucleic acid segments.

In addition, the text which follows is suggested for consolidating these two paragraphs in a manner that focuses their meaning and intent:

Genetically modified organisms containing two or more nucleic acid segments, regardless of origin, may necessitate a complex risk analysis. Preliminary analysis should consider the risk associated with original source sequences taking into account their virulence, pathogenicity, transmissibility, etc. Additional risk assessment analysis must include the additive effects of the greater of the associated risks. Because there may be unanticipated consequences of multiple genetic modifications, the possibility of greater or lower risk-hazard than expected must be considered. It may be necessary to test the final modified organisms with *in vitro* and/or *in vivo* studies under the initial assumption that they are a high-risk hazard.” As a result of these risk analysis determinations, defined acceptable risks must be developed and promulgated.

Comment regarding Section III-A-1.

The American biological Safety Association endorses the ASM comments regarding Section III-A-1.

Proposed Changes to Section III-C: The proposed text for this section is, “For an experiment involving the deliberate transfer of recombinant or synthetic nucleic acids into human research participants (human gene transfer), no research participant shall be

enrolled (see definition of enrollment in Section I-E-7) until the RAC review process has been completed (see Appendix M-I-B, RAC Review Requirements).

Use of the term, “human gene transfer” is appropriate in the existing NIH Guidelines. However, its use would not cover “non-coding” sections such as shRNA and antisense RNA as well as other current and future structures. All of these constructs cannot be considered to be genes. Use of the terms “therapeutic nucleic acid transfer” or “clinical recombinant nucleic acid” would be more appropriate, or consider the use of another term that is inclusive of synthetic nucleic acids in its scope. Since the term, “human gene transfer” is used multiple times in the Guidelines, any alternative term should be consistently used throughout the Guidelines and not just in this section. This text should also note coverage of the Guidelines in veterinary applications of these materials.

The proposed changes to the NIH Guidelines demonstrate a clear case for the need for applied biological safety research and training across a broad range of recombinant and synthetic nucleic acid issues. Research results would provide evidence-based data and guidance that will help in determining risk assessments and appropriate training to different user groups. NIH or OBA should seek funding to conduct research to characterize risks associated with investigations considerate of the NIH Guidelines, as well as funding to help train investigators and staff at all levels to more safely and effectively conduct these investigations.

ABSA would welcome the opportunity to assist OBA in any restructuring and revisions to the NIH Guidelines that may be under consideration. Many technical and administrative issues have changed since the NIH Guidelines were initially drafted. Restructuring and revisions of this document could facilitate its use and could better address some of the current issues which researchers are now facing.

We appreciate this comment opportunity for these proposed revisions.

Sincerely,

A handwritten signature in black ink that reads "Robert P. Ellis". The signature is written in a cursive style with a clear, legible font.

Robert Ellis, PhD. CBSP
President

American Biological Safety Association