



Proposed Revisions to the *NIH Guidelines*

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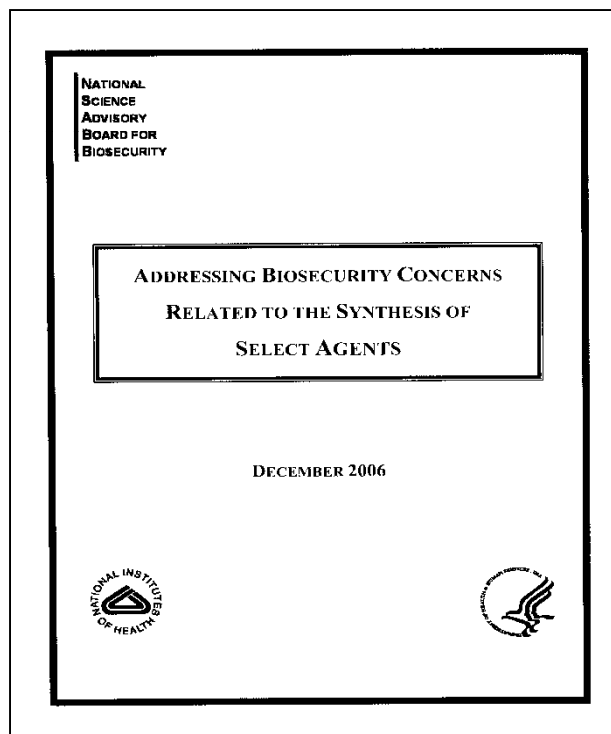


Proposed Revisions

- **Section I-B - Synthetic Nucleic Acids**
- **Section III-E-1 - The 2/3^{rds} Rule**
- **Section III-E-3 - Cross Breeding of BL1 Transgenic Rodents**



NSABB Report



http://oba.od.nih.gov/biosecurity/biosecurity_documents.html



NSABB Findings

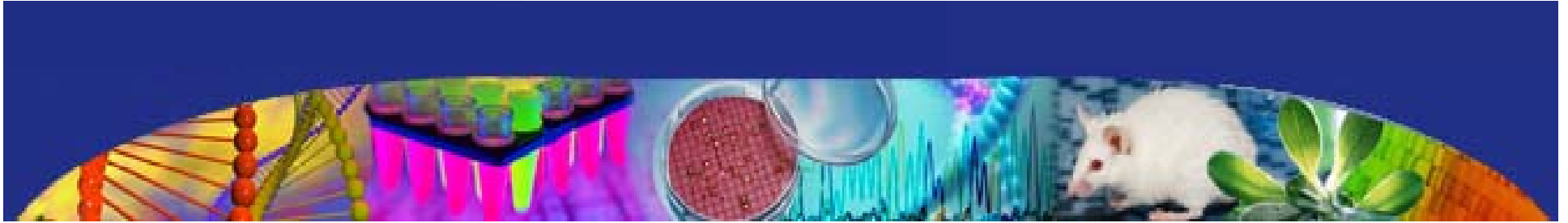
- **Some practitioners of synthetic genomics are:**
 - **Educated in disciplines that do not routinely entail formal training in biosafety; and**
 - **Uncertain about when to consult an Institutional Biosafety Committee (IBC).**
- **There is a need for biosafety principles and practices applicable to synthetic genomics.**



Current Biosafety Guidelines

- ***NIH Guidelines* are limited to synthetic DNA joined by recombinant methods**
 - Does not cover synthetic DNA that is synthesized *de novo*
 - Does not cover synthesized RNA viruses

- **Biosafety in Microbiological and Biomedical Laboratories Manual (BMBL)**
 - Agent specific, not technology driven
 - References *NIH Guidelines* with respect to synthetic recombinant molecules



Recombinant DNA Advisory Committee

- **Considered the application of the *NIH Guidelines* to synthetic biology**
 - To what degree is this technology covered?
 - Does the scope need to be modified to capture synthetic biology research?
- **Develop recommendations regarding principles and procedures for risk assessment and management of research involving synthetic biology**



Synthetic Nucleic Acids Existing Language

- ***NIH Guidelines for Research Involving Recombinant DNA Molecules***
 - **Molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or**
 - **Molecules that result from the replication of those described above**



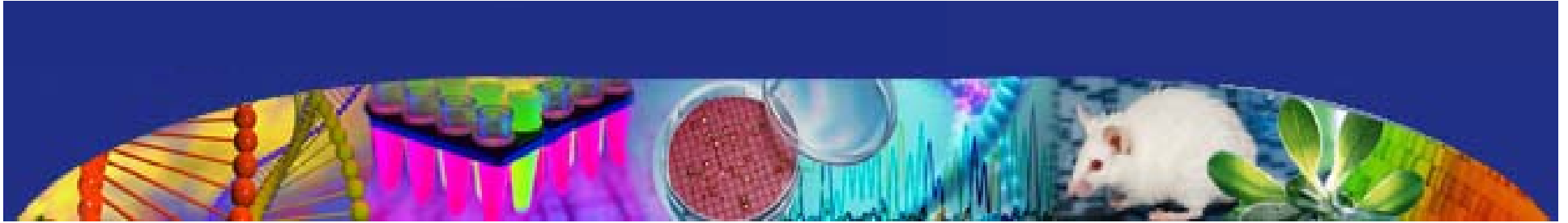
Overall Approach

- **Capture the same products made by synthetic techniques that are currently covered under the *NIH Guidelines* for recombinant DNA research provided the same biosafety concerns are raised**
 - **Level of review based on risk not technique**
- **Recognize that all not all future scientific developments can be anticipated, so that the *NIH Guidelines* will need periodic review and updating**



Section I-B. Definition of Recombinant DNA Molecules

- (i) Recombinant nucleic acid molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell,**
- (i) Synthetic nucleic acid molecules that are chemically, or by other means, synthesized or amplified, including those that are chemically or otherwise modified but can base pair (bind) with naturally occurring nucleic acid molecules**
- (iii) molecules that result from the replication of those described in (i) or (ii) above.**



Non-replicating Synthetic NAs: Basic Research

- **Exposure in the lab to a low dose of non-replicating synthetic nucleic acid sequence is considered low risk**
 - **No replication if the NAs enter a cell**
 - **No spread in the environment if released**
 - **Exposure similar to that of a chemical exposure; however nucleic acids are not toxic in and of themselves**



Basic Research with Synthetic Nucleic Acids

- **New Section F-1 will exempt from the *NIH Guidelines* those synthetic nucleic acids that:**
 - **can neither replicate nor generate nucleic acids that can replicate in a **any** living cell [e.g. oligonucleotides or other synthetic NAs that do not contain an origin of replication or contain elements known to interact with either DNA or RNA polymerase], and**
 - a) **are not designed to integrate into DNA, and**
 - b) **do not produce a toxin that is lethal for vertebrates at an LD50 < 100 nanograms, and**
 - c) **are not deliberately transferred into one or more human research participants (see Section III-C and Appendix M).**



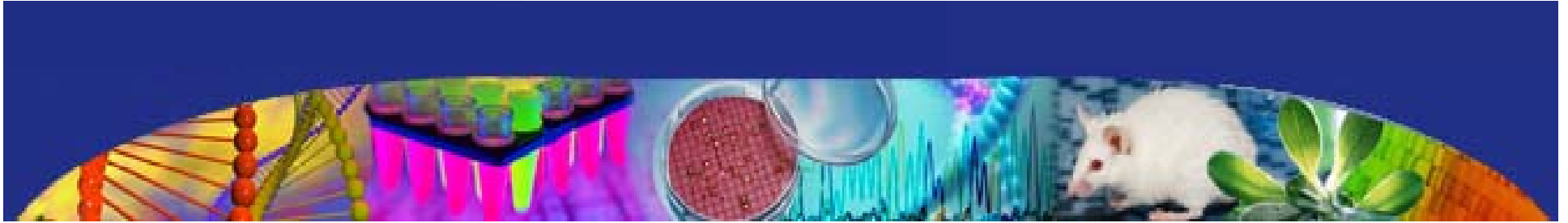
Human Gene Transfer

- **Many human gene transfer trials use replication incompetent vectors; however, safety risks often arise from other factors that are not dependent on replication including transgene effects, insertional mutagenesis, and immunological responses**
- **Doses and routes used in human gene transfer potentially increase risks compared to those anticipated for inadvertent lab exposure**
- **Human gene transfer often raises unique scientific, medical and ethical issues that warrant transparent oversight**



Non-Vector vs. Vector Constructs

- **Comments agreed that vector constructs are human gene transfer, whether made synthetically or by recombinant means**
- **Considerable debate by RAC as to whether to include synthetic RNA and DNA not delivered by a traditional viral, plasmid or bacterial vectors**



Public Comments – March 2009 Proposal

- **Urged RAC and OBA to differentiate synthetic RNA and DNA oligonucleotide agents from gene transfer agents that use vectors based on the following characteristics:**
 - ❑ **short half-life with more predictable pharmacokinetics**
 - ❑ **lack of ability to integrate into the genome**
 - ❑ **lack of replication or potential for inadvertent replication due to mobilization or recombination**
 - ❑ **lack of a transgene for coding a protein**



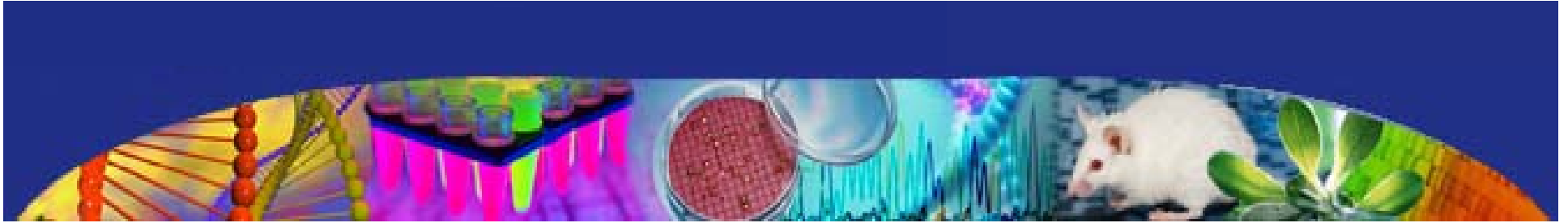
Next Steps

- **Implement changes to *NIH Guidelines* to cover synthetic nucleic acids**
- **Limit the changes to human gene transfer to cover synthetic vectors that are equivalent to recombinant vectors**



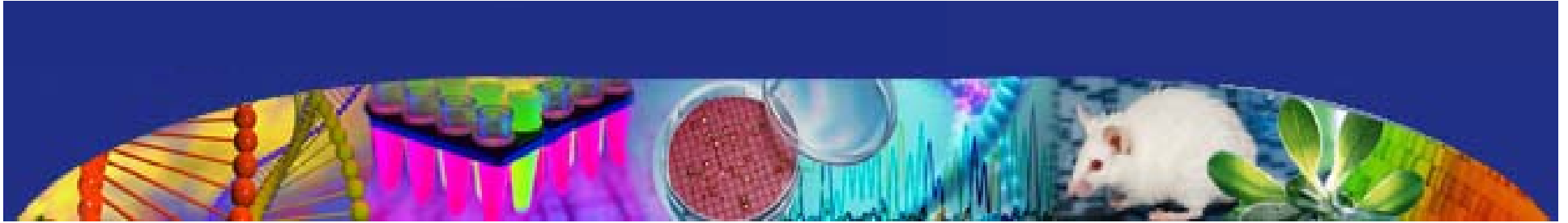
Section III-C-1 : Human Gene Transfer

- **Human gene transfer includes all experiments involving the deliberate transfer of either:**
 - 1) **Recombinant DNA, or DNA or RNA derived from recombinant DNA or**
 - 2) **Synthetic DNA or RNA that:**
 - **Contains greater than 100 nucleotides or base pairs in total; or**
 - **Have characteristics than enable integration into the genome; or**
 - **Are known to replicate in a cell; or**
 - **Are known to be transcribed or translated**



Section II-E-1

Experiments Involving the Formation of Recombinant DNA Molecules Containing No More than Two-Thirds of the Genome of any Eukaryotic Virus



Section II-E-1

- **Current language allows certain tissue culture experiments to be conducted at BL1 if:**
 - **No more than 2/3rds of full viral genome is present, AND**
 - **The cells lack helper virus**



Original Proposed Changes

- Reduce the two thirds requirement to ONE-HALF
 - Public comment reflected concern that it may be possible to generate a functional virus containing less than $2/3$ of the genome



Revised Proposed Changes

- Tissue culture experiments in which less than one-half of any viral genome is present

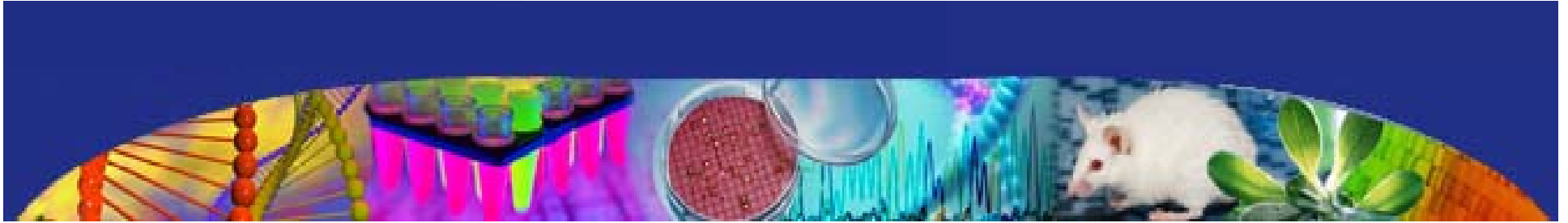
OR

- Where more than one half of a viral genome is present as long as the function of critical viral genes is sufficiently understood to allow a determination that a complete deletion in one or more essential viral capsid, envelope or polymerase genes required for cell-to-cell transmission of viral nucleic acids will effectively impair viral replication



Revised Proposed Changes

- The deletion must be designed such that it is not possible to rescue critical functions through homologous recombination



Revised Proposed Changes

- **Will apply only to RG 3 and 4 viruses as the *NIH Guidelines* already exempt research with less than one-half of the genome of a RG 1 or 2 virus (See Appendix C-1 and C-1-A)**



Cross Breeding BL1 Transgenic Rodents (or WT x TG)



X



Section III-E (IBC notification upon initiation)



Current *NIH Guidelines* Section III-E-3 Experiments Involving Transgenic Rodents

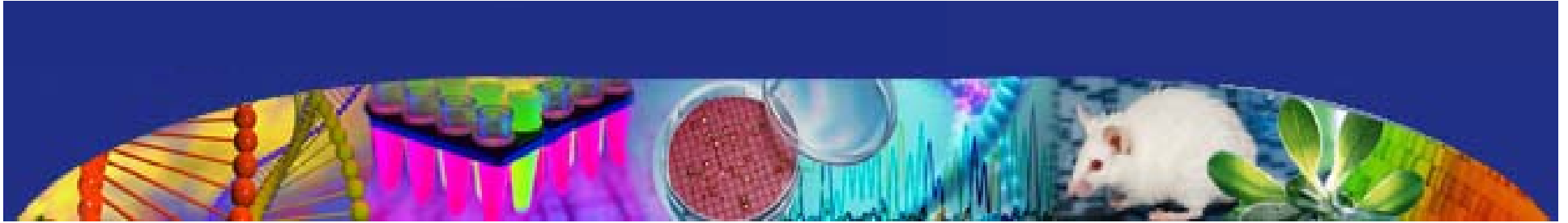
- **Experiments that require BL 1 containment involving the generation of rodents in which the animal's genome has been altered by stable introduction of recombinant DNA, or DNA derived therefrom, into the germ-line (transgenic rodents) may be initiated upon registration with the IBC**

- **Under the *NIH Guidelines*, “generation” of a transgenic rodent includes mating between two different transgenic rodents or mating of a transgenic rodent and a non-transgenic rodent if the purpose is to create a new transgenic rodent**
 - **Breeding of two identical transgenic rodents to maintain a line is not subject to this section of the *NIH Guidelines***



Impetus for Considering an Exemption for Mating of Certain Transgenic Rodents

- **Transgenic rodents that may be contained under BL1 conditions do not pose an appreciable biosafety risk to humans**
- **The *NIH Guidelines* currently exempts the purchase or transfer of transgenic rodents that require BL1 containment (Appendix C-VI)**



Impetus For Considering an Exemption for Mating of Certain Transgenic Rodents

- **The overwhelming majority of matings of transgenic rodents that require BL1 containment will result in a rodent that can be housed at BL1 and would therefore not pose an appreciable risk to human health**
- **While each registration is not a significant burden, the total number of registrations required leads to an administrative burden on the IBC and researchers that does not appear to be commensurate with the biosafety risk**



Proposed Exemption: Mating of Transgenic Rodents

Appendix C–VII.

Generation of BL1 Transgenic Rodents via Breeding

- **The mating of two different transgenic rodents or the mating of a transgenic rodent with a non-transgenic rodent with the intent of creating another transgenic rodent that requires BL1 containment, will be exempt from the NIH Guidelines if:**
 - **Both parental rodents require BL1 containment,**



Proposed Exemption: Mating of Transgenic Rodents

AND

- **Each parental transgenic rodent does not contain any one of the following genetic modifications:**
 - a) **More than 50% of the genome of an exogenous virus from a single family; or**
 - b) **Expression of the transgene is under the control of a gammaretroviral long terminal repeat;**



Proposed Exemption: Mating of Transgenic Rodents

AND

- **It is anticipated that the transgenic rodent that results from this mating will not:**
 - a) **Contain more than 50% of an exogenous viral genome from a single family**



Comments Received in Response to FR Notice

- **9 comments received; all supportive**
- **One comment asked for clarification of how much gammaretroviral LTR sequence must be present to not be exempt**

In the final FR notice, additional will be added to clarify sufficient gammaretroviral LTR sequence to control expression of the transgene (not smaller fragments of homologous sequence not acting as a promoter)



RAC Discussion

March 2010

June 2010

September 2010

http://oba.od.nih.gov/rdna_rac/rac_past_meetings_2000.html



Major Action Language Update

**March 4, 2009 Federal Register, Volume 74,
Number 41**

- **Proposed revising the criteria for determining when introduction of a drug resistance trait into a microorganism must be reviewed and approved by the NIH Director.**
- **Proposed amendment also contained additional language requiring consideration of the utility of the drug in certain subpopulations.**



Major Action Language Update

Where this stands now?

- Retaining original language
- Adding clarifications regarding use of drugs in subpopulations
- Exploring a mechanism for “same experiment” submissions
 - See June and December 2009 RAC meeting archive for more details

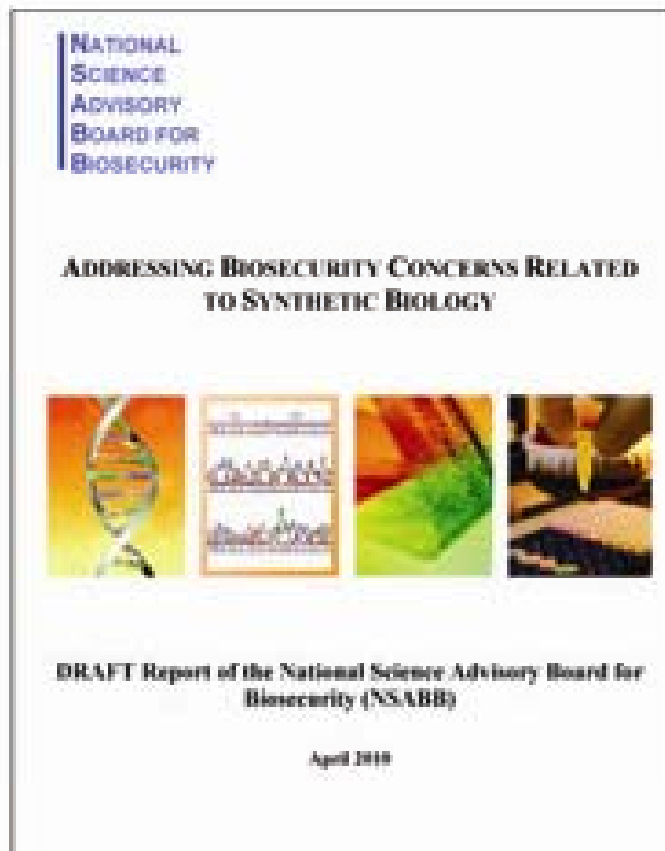


What else is new?





New NSABB Report





Dual Use Research Educational DVD





Office of Biotechnology Activities

*DOES YOUR
RESEARCH
HAVE DUAL USE
POTENTIAL?*



NATIONAL INSTITUTES OF HEALTH

Dual Use Research Educational Brochure

http://www.biosecurityboard.gov

The screenshot shows a Mozilla Firefox browser window displaying the website for the Office of Biotechnology Activities (OBA) under the Office of Science Policy - National Institutes of Health. The browser's address bar is empty, and the search engine is set to Google. The website header includes the NIH logo and the text "OFFICE OF SCIENCE POLICY - National Institutes of Health". Below this, the main heading is "Office of Biotechnology Activities". A navigation menu includes links for "Home", "Recombinant DNA", "Genetics, Health, Society", "Dual Use Research" (which is highlighted), and "Clinical Research Policy". On the right side of the header, there are links for "Help", "Sitemap", and "Contact us", along with a search box and a "Printer Friendly Page" link. The main content area is titled "Dual Use Research" and contains the following text: "The Dual Use Research Program is a focal point for the development of policies addressing life sciences research that yield information or technologies with the potential to be misused to threaten public health or other aspects of national security." It also mentions OBA's activities to address such "dual use" research, including convening and managing the **National Science Advisory Board for Biosecurity (NSABB)**. A list of purposes for the NSABB is provided: "The purposes of the NSABB are to: • Advise the Federal government on strategies to minimize the risks and harm that could result from malevolent use of legitimate research. • Support development of Federal and institutional oversight guidelines. • Promote awareness in the research community about the dual-use issue. • Foster international collaboration on issues related to dual-use research." On the left side of the main content area, there is a sidebar with links for "About NSABB", "News and Events", "NSABB Meetings", "Frequently Asked Questions", "NSABB Documents", and "Participating Agencies". The browser's taskbar at the bottom shows the Start button, several open applications, and the system clock displaying 11:01 AM.

Terminé



NEXT NSABB Meeting

October 19-20, 2010

NIH Main Campus,

Bldg. 31, Floor 6C, Room 10,

Bethesda, MD



Awareness of Incident Reporting Requirements

- **Incorporate incident reporting requirements into training program**

Report within 30 days to NIH OBA any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses



Awareness of Incident Reporting Requirements

- Report immediately to NIH OBA certain incidents described in Appendix G-II

Appendix G-II-B-2-k. Spills and accidents which result in overt exposures to organisms containing recombinant DNA molecules are **immediately reported** to the Institutional Biosafety Committee and NIH/OBA.

Appendix G-II-C-2-q. Spills and accidents which result in overt or potential exposures to organisms containing recombinant DNA molecules are **immediately reported** to the Biological Safety Officer, Institutional Biosafety committee, and NIH/OBA.



Incident Reporting FAQ

National Institutes of Health • Office of Biotechnology Activities

Information for Labs Conducting Recombinant DNA Research

Reporting of Incidents Involving Recombinant DNA to the NIH Office of Biotechnology Activities (OBA)

- **What kinds of incidents involving recombinant DNA must be reported to the NIH OBA?**

The *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* states that "...any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses" must be reported to NIH OBA within 30 days. Certain types of accidents must be reported on a more expedited basis. Spills or accidents in BL2 laboratories resulting in an overt exposure must be immediately reported to NIH OBA. Spills or accidents occurring in high containment (BL3 or BL4) laboratories resulting in an overt or potential exposure must be immediately reported to NIH OBA.
- **How serious must a problem be to warrant reporting to OBA?**

Any spill or accident involving recombinant DNA research of the nature described above or that otherwise leads to personal injury or illness or to a breach of containment must be reported to OBA. These kinds of events might include skin punctures with needles containing recombinant DNA, the escape or improper disposition of a transgenic animal, or spills of high-risk recombinant materials occurring outside of a biosafety cabinet. Failure to adhere to the containment and biosafety practices articulated in the *NIH Guidelines* must also be reported to OBA.

Minor spills of low-risk agents not involving a breach of containment that were properly cleaned and decontaminated generally do not need to be reported. OBA should be consulted if the Institutional Biosafety Committee (IBC), investigator, or other institutional staff are uncertain whether the nature or severity of the incident warrants reporting; OBA can assist in making this determination.
- **Who is responsible for reporting incidents involving recombinant DNA to NIH OBA?**

Under the *NIH Guidelines* incident reporting is articulated as a responsibility of the Institution, IBC, Biological Safety Officer, and Principal Investigator. Institutions have the discretion to determine which party should make these reports, and one report for each incident or set of information is generally sufficient.

6705 Rockledge Drive, Suite 750, Bethesda MD 20892-7985 • Tel (301)496-9838 • Fax (301)496-9839
Email: oba@od.nih.gov • <http://www4.od.nih.gov/oba>



Incident Reporting Template

Template for Reporting Incidents Involving Recombinant DNA to the NIH Office of Biotechnology Activities (OBA)

The *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* states that "...any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses" must be reported to NIH OBA within 30 days. Certain types of incidents must be reported on a more expedited basis. Spills or accidents in BL2 laboratories resulting in an overt exposure must be immediately reported to NIH OBA. Spills or accidents occurring in high containment (BL3 or BL4) laboratories resulting in an overt or potential exposure must be immediately reported to NIH OBA.

This template is intended to facilitate the reporting of incidents that occur during the conduct of research subject to the *NIH Guidelines*. You may download this template as a Word document and the fields will expand according to the amount of text entered. Use of this template is not required and other formats may be acceptable.

**A separate template for reporting Human Gene Transfer Adverse Events is available at:
http://www4.od.nih.gov/oba/RAC/Adverse_Event_Template.doc**

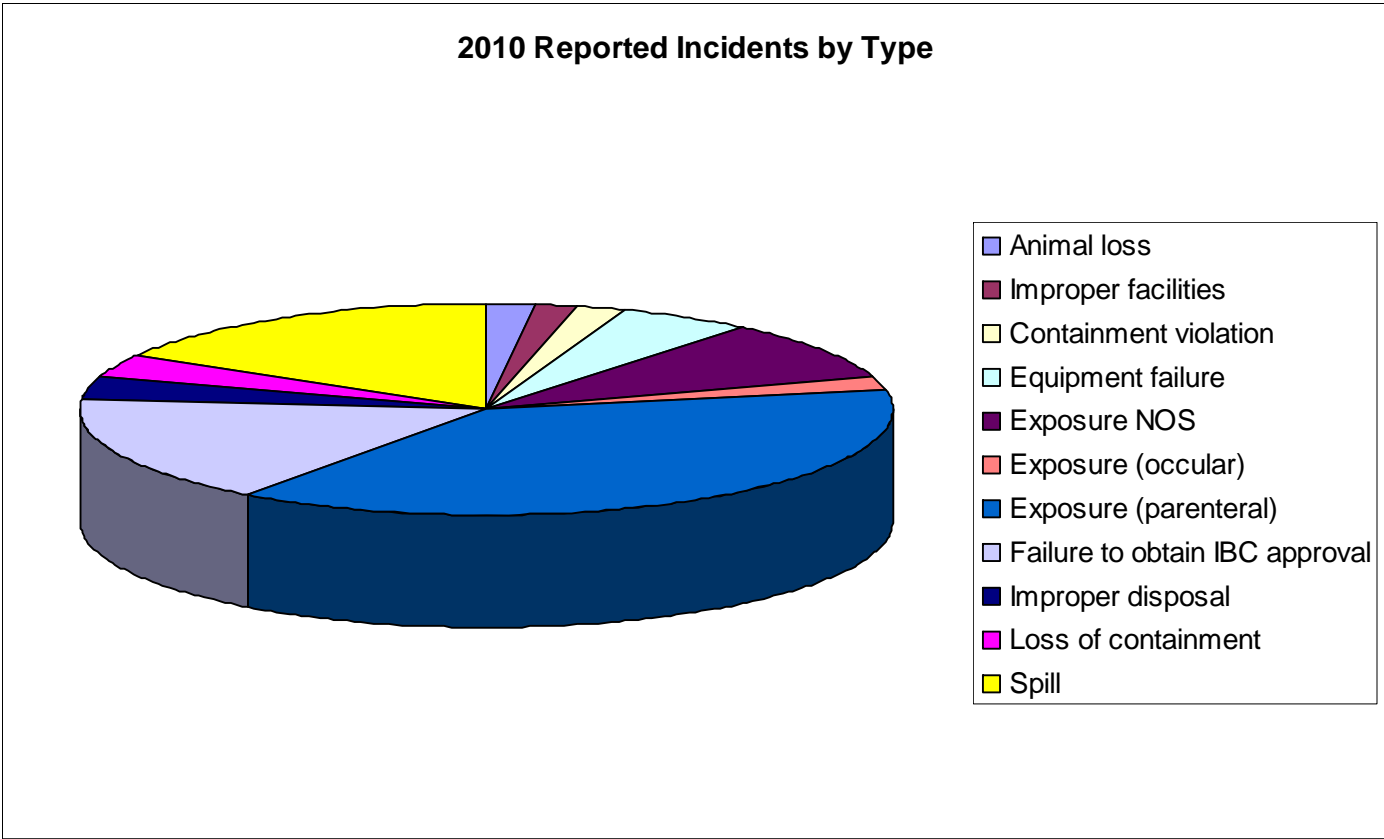
Please note that submitting this completed template to NIH OBA does NOT fulfill the reporting requirements of other agencies. You should verify with the other parties to whom you must report whether the use of this template is acceptable.

Completed reports may be sent via U.S. mail, courier service, e-mail, or facsimile to:

**Attention: Incident Reports
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, Maryland 20892-7985
(For all non-USPS deliveries use Zip Code 20817)
Telephone 301-496-9838
Fax 301-496-9839
E-mail: oba@od.nih.gov**



Incidents by Type for 2010



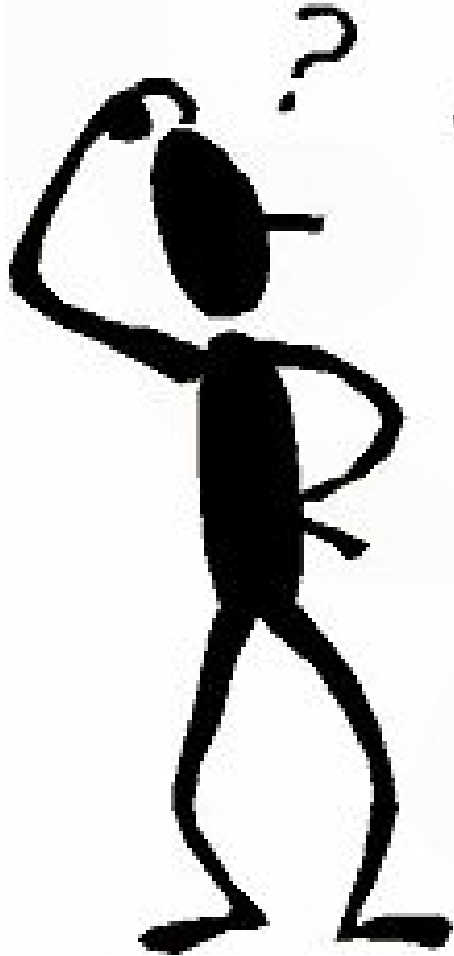


Save the Date!

IBC Professional Development Conference

June 12-14, 2011
San Diego





Questions?