


National Institutes of Health  
Office of Biotechnology Activities


# **What's New from NIH OBA?**

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# **What's New from NIH OBA?**

- Recent Amendments to the  
*NIH Guidelines***
- Incident Reporting – Some  
Lessons (Re)Learnt**
- New Educational Materials**



## Recent Amendments to the *NIH Guidelines*

- **Research with synthetic nucleic acid molecules**
  - What is covered and what isn't




## Impetus for Amending the Scope of the *NIH Guidelines*

- **Capture the same products made by synthetic techniques that raise comparable biosafety considerations to recombinant agents covered under the *NIH Guidelines***



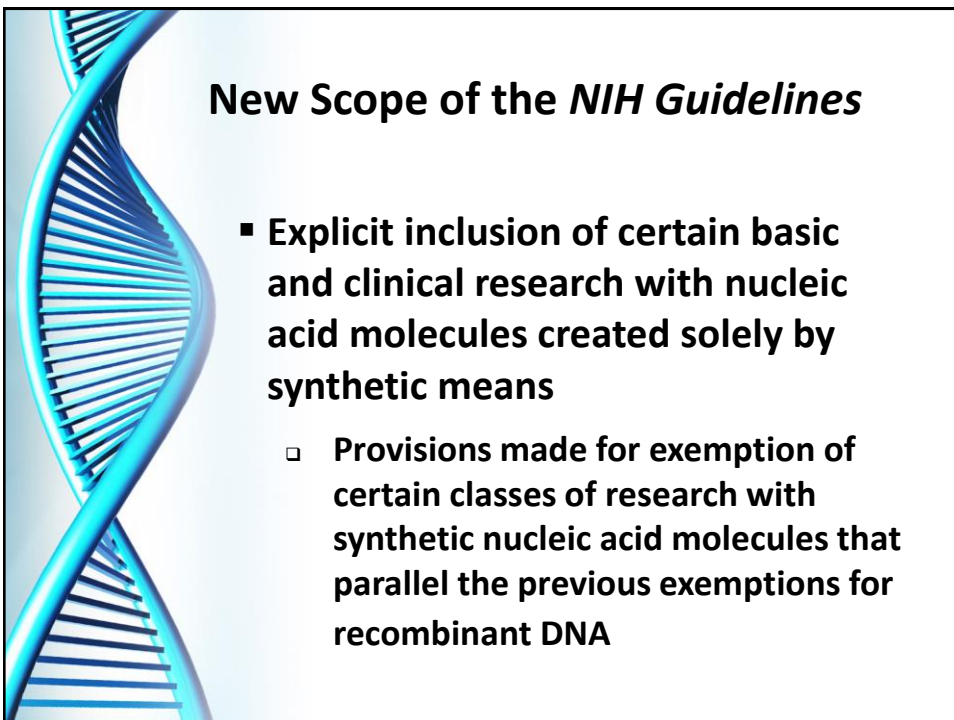
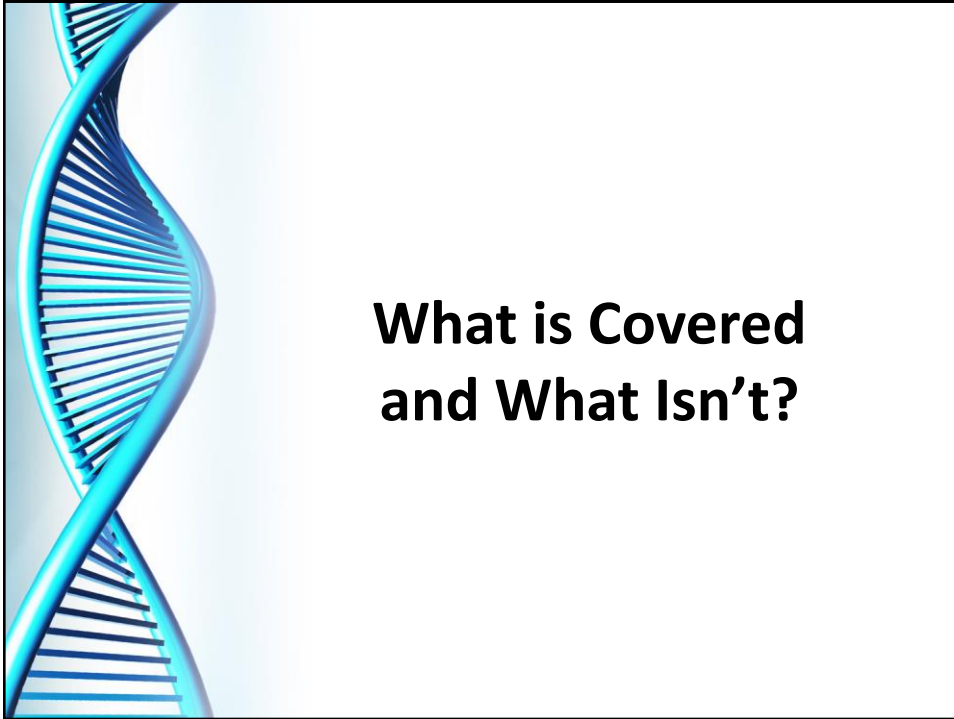
## New Title of the *NIH Guidelines*

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

## Specific Sections of the *NIH Guidelines* That Have Been Amended

<p>Section I.</p> <p>Section I-B.</p> <p>Section I-C.</p> <p>Section II-A-3.</p> <p>Section III-C.</p>	<p>Scope of the <i>NIH Guidelines</i></p> <p>Definition of Recombinant DNA</p> <p>General Applicability</p> <p>Comprehensive Risk Assessment</p> <p>Experiments involving the Deliberate Transfer of Recombinant DNA, or DNA or RNA Derived from Recombinant DNA, into One or More Human Research Participants</p>
<p>Section III-F.</p> <p>Section IV-A.</p>	<p>Exempt Experiments</p> <p>Policy</p>





## Scope

- The *NIH Guidelines* now apply (unless otherwise exempted) to both recombinant and synthetically derived nucleic acid molecules, including those that are chemically or otherwise modified analogs of nucleotides (e.g., morpholinos)




## Morpholinos

(From *Wikipedia*)

Morpholinos are synthetic molecules that are the product of a redesign of natural nucleic acid structure.


Usually 25 bases in length, they bind to complementary sequences of RNA by standard nucleic acid base-pairing.

In terms of structure, the difference between Morpholinos and DNA is that, while Morpholinos have standard nucleic acid bases, those bases are bound to morpholine rings instead of deoxyribose rings and linked through phosphorodiamidate groups instead of phosphates.



## Exemptions: Section III-F-1

- **Exempts those synthetic nucleic acid molecules that:**
  - (1) can neither replicate nor generate nucleic acids that can replicate in any living cell (e.g., oligonucleotides or other synthetic nucleic acids that do not contain an origin of replication or contain elements known to interact with either DNA or RNA polymerase), and
  - (2) are not designed to integrate into DNA, and
  - (3) do not produce a toxin that is lethal for vertebrates at an LD50 of less than 100 nanograms per kilogram body weight



## Exemptions: Section III-F-1

- **Example:** An investigator wishes to use a synthetic nucleic acid molecule that has no origin of replication, doesn't integrate and does not encode for a toxin, however it has been encapsulated in a liposome
- The IBC thinks the molecule could be exempt under III-F-1 but wonders if it may not be because it is encapsulated. They remember that another part of the Guidelines states that molecules are exempt provided they have not been modified or manipulated (e.g., encapsulated into synthetic or natural vehicles) to render them capable of penetrating cellular membranes






## Section III-F-2

- **Exempts the following experiments:**
  - **Those molecules that are not in organisms, cells or viruses and that have not been modified or manipulated (e.g., encapsulated into synthetic or natural vehicles) to render them capable of penetrating cellular membranes**




## Exemptions: Section III-F-1

- **If the molecule is exempt under III-F-1, it's subsequent use is also exempt, so even though it is encapsulated in a liposome it remains exempt (the III-F-2 language regarding modification does not apply to an already exempt molecule)**



### **Exemptions: Section III-F-3**


- **Does the synthesis of naturally occurring organisms fall under the *NIH Guidelines*?**



### **Exemptions: Section III-F-3**

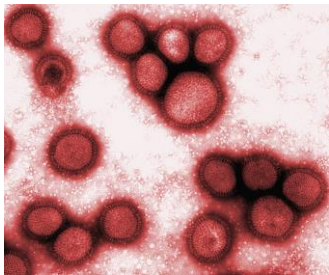

- **No - Section III-F-3 exempts experiments that consist solely of the exact recombinant or synthetic nucleic acid sequence from a single source that exists contemporaneously in nature**






## Is the Synthesis of Naturally Occurring Organisms Covered?

- **Note - this exemption is limited to those nucleic acid sequences from organisms that exist outside of a laboratory setting. Research with nucleic acid sequences for organisms that do not currently exist in nature outside of a laboratory, for example, an identical copy of the 1918 H1N1 influenza virus is not exempt**


## Another Example: Exempt under III-F-3?

- **RNA derived from a tumor sample of a participant in a human gene transfer study is to be amplified and transcribed *in vitro* (and contains more than 100 nucleotides)**
  - **Would use of this constructs in a clinical trial be exempt under Section III-F-3 because it “....consists solely of the exact recombinant or synthetic nucleic acid sequence from a single source that exists contemporaneously in nature”**



### Another Example: Exempt under III-F?

- No - Remember that there are 'exceptions' to the exemptions – If a molecule is being used in a human gene transfer trial it will be covered under section III-C
- If work is covered under III-A, III-B, or III-C, and III-F, then the exemption does not apply because III-A, III-B and III-C trumps III-F



### Other Changes

- Throughout the *NIH Guidelines*, the term "recombinant DNA molecules" has been replaced with "recombinant or synthetic nucleic acid molecules," which encompasses research with either recombinant or synthetic or both types of nucleic acid molecules



## When did the Amended *NIH Guidelines* Go Into Effect?

- New requirements were effective six months after the date of publication of the changes in the *Federal Register* (September 5, 2012):
  - All ongoing and proposed experiments that are newly subject to the amended *NIH Guidelines* should have been registered by the Principal Investigator with the IBC by March 5, 2013



## Implementation of Amended *NIH Guidelines*

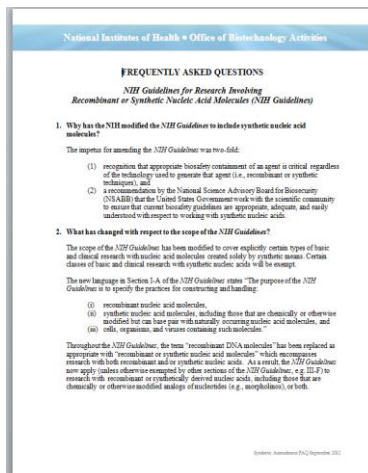
- Institutions should by now have developed new procedures and reached out to investigators performing research that is newly covered under the *NIH Guidelines*
- Composition of the IBC does not need to change, but institutions may choose to add to the membership depending upon their research portfolio

## Additional Resources


- **Additional Information on the changes to the *NIH Guidelines* can be found in the published *Federal Register Notice 77 FR 54584* (September 5, 2012) which is available at:**

<http://www.archives.gov/federal-register/index.html>

## Additional Resources




[http://oba.od.nih.gov/rdna/rdna\\_faq\\_list.html](http://oba.od.nih.gov/rdna/rdna_faq_list.html)



### Incident Reporting Requirements under the *NIH Guidelines*


- Under the *NIH Guidelines* "...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 immediately reported to NIH OBA:
  - ❑ Spills or accidents in BL2 laboratories resulting in an overt exposure
  - ❑ Spills or accidents occurring in high containment (BL3 or BL4) laboratories resulting in an overt or potential exposure





## Importance of Incident Reporting

- Keeps institutions aware of and accountable for safety-related problems
- Provides OBA an opportunity to educate institutions about optimal responses to safety events
- Allows OBA to identify patterns of safety problems at particular institutions, possibly pointing to a need for
  - ❑ Broad-based training
  - ❑ Interventions in particular laboratories



## Importance of Incident Reporting

- Allows OBA to identify patterns of safety problems nationwide which may need broader educational outreach
  - ❑ Issues with particular practices
  - ❑ Safety challenges with particular agents
  - ❑ Points of emphasis in OBA educational programs
  - ❑ Areas where the *NIH Guidelines* may need clarification or amendment



# Incident Reporting FAQs

National Institutes of Health · Office of Biotechnology Activities

## *Frequently Asked Questions for Labs Conducting Recombinant or Synthetic Nucleic Acid Research*

Reporting of Incidents Related to Research Subject to the  
NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acids to the  
National Institutes of Health (NIH) Office of Biotechnology Activities (OBA)

### 1. What kinds of incidents involving recombinant DNA must be reported to the NIH OBA?

The *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid 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.

[http://oba.od.nih.gov/oba/ibc/FAQs/FAQs\\_about\\_Incident\\_Reporting.pdf](http://oba.od.nih.gov/oba/ibc/FAQs/FAQs_about_Incident_Reporting.pdf)

# NIH 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.

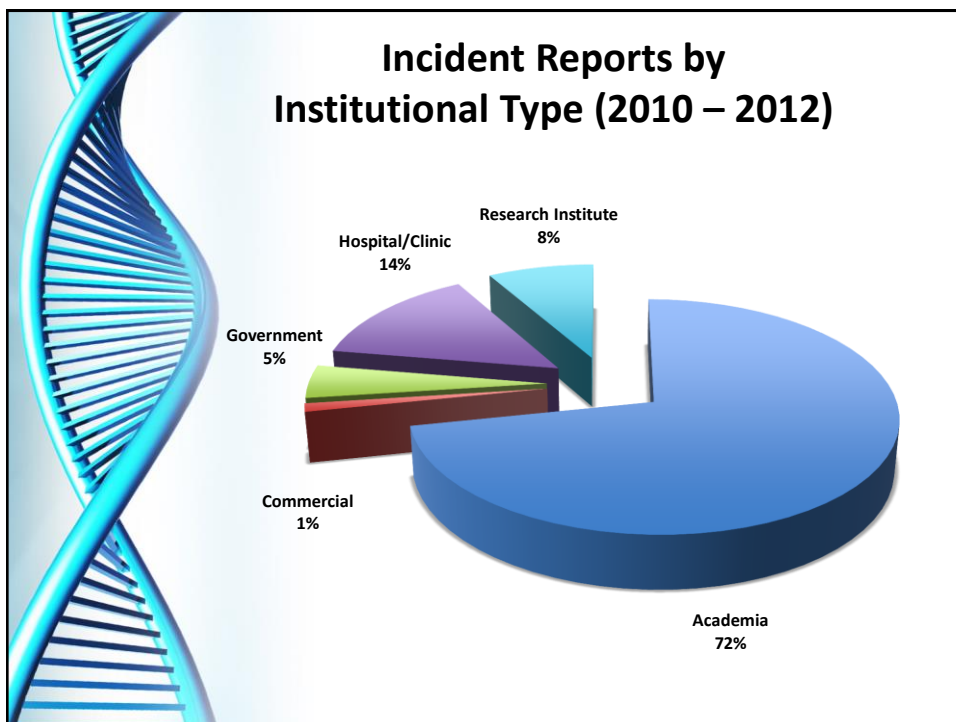
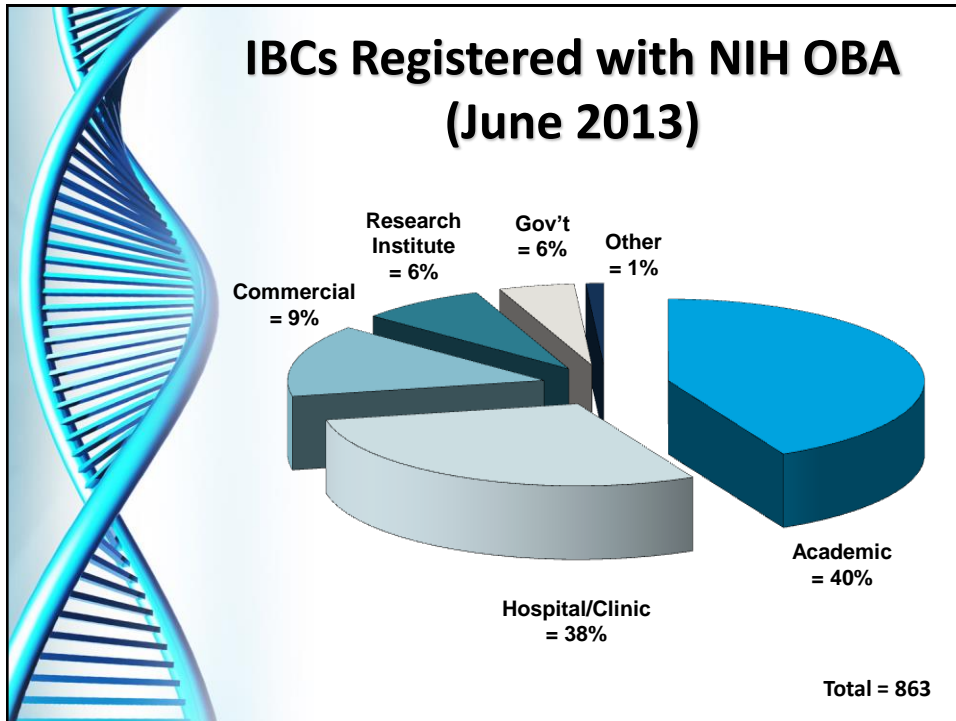
A separate template for reporting Human Gene Transfer Adverse Events is available at:  
[http://www4.od.nih.gov/oba/RAC/Adverse\\_Event\\_Template.doc](http://www4.od.nih.gov/oba/RAC/Adverse_Event_Template.doc)

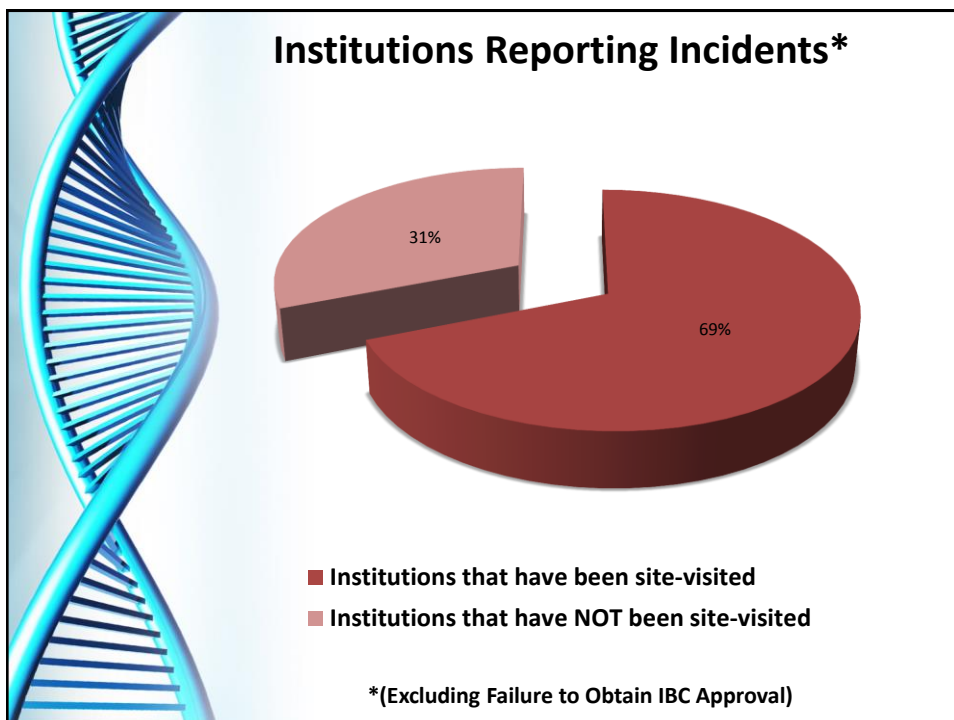
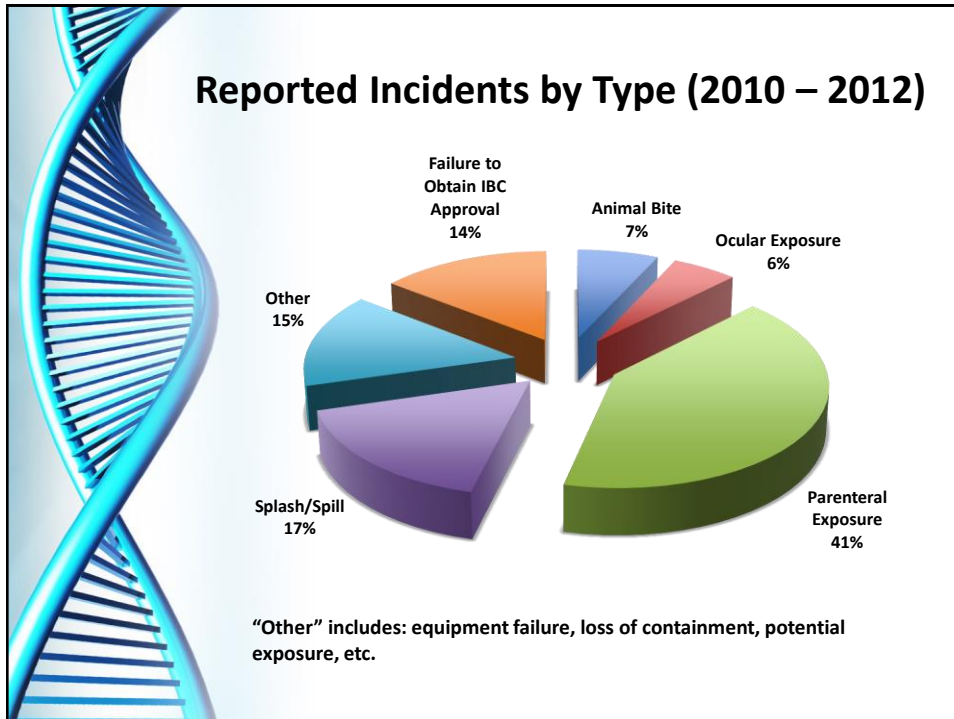
Please note that submitting this completed template to NIH OBA does NOT fulfill the reporting requirements of other agencies. You should verify with the other parties to whom you must report whether the use of this template is acceptable.

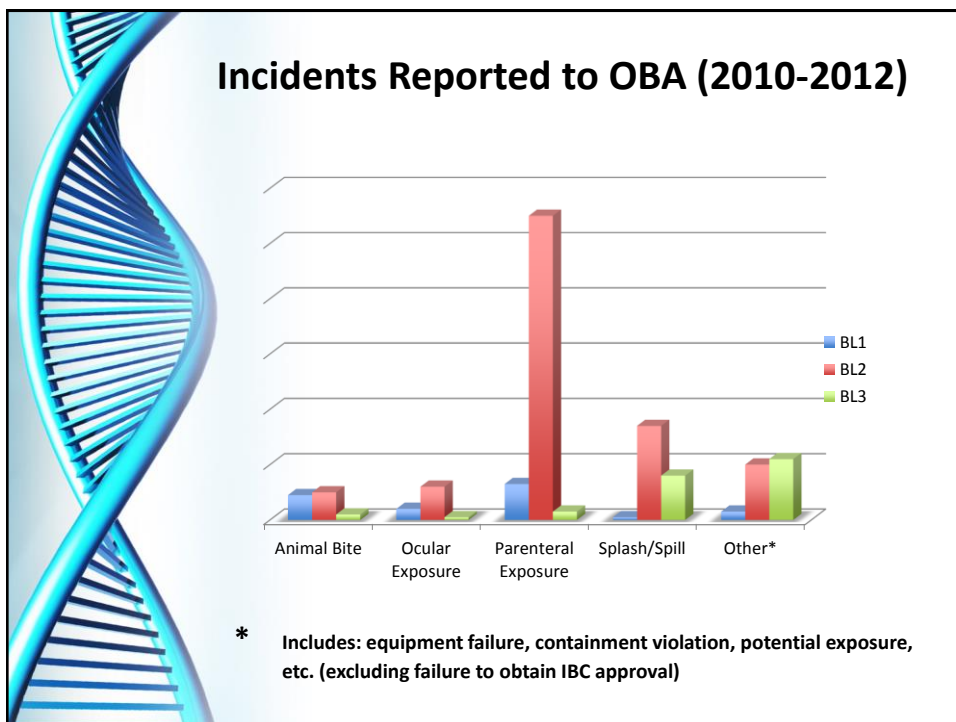
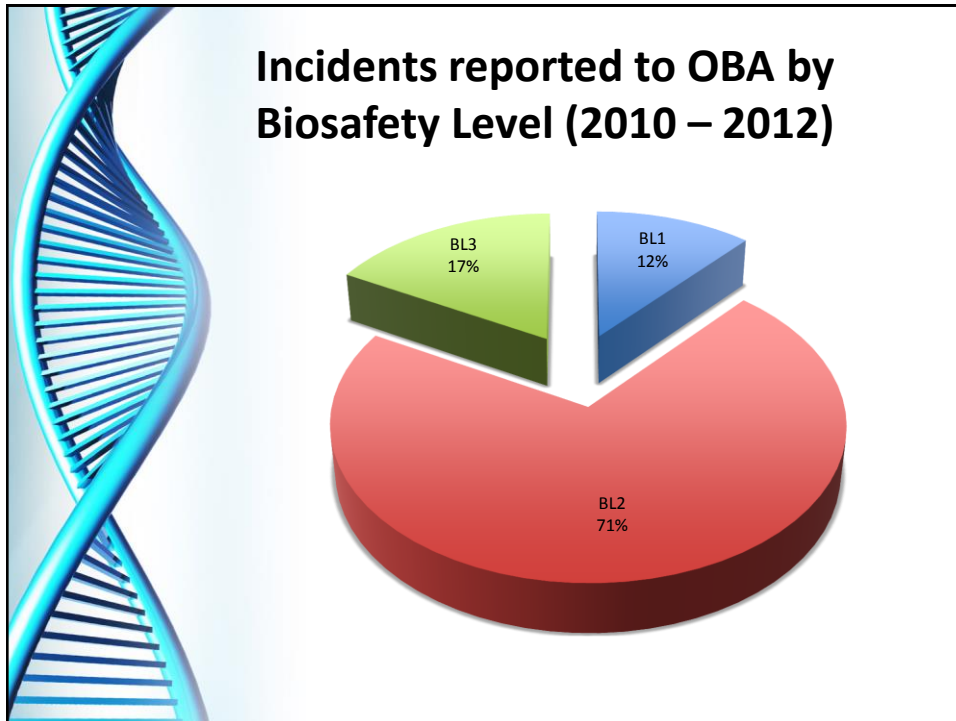
Completed reports may be sent via U.S. mail, courier service, e-mail, or facsimile to:

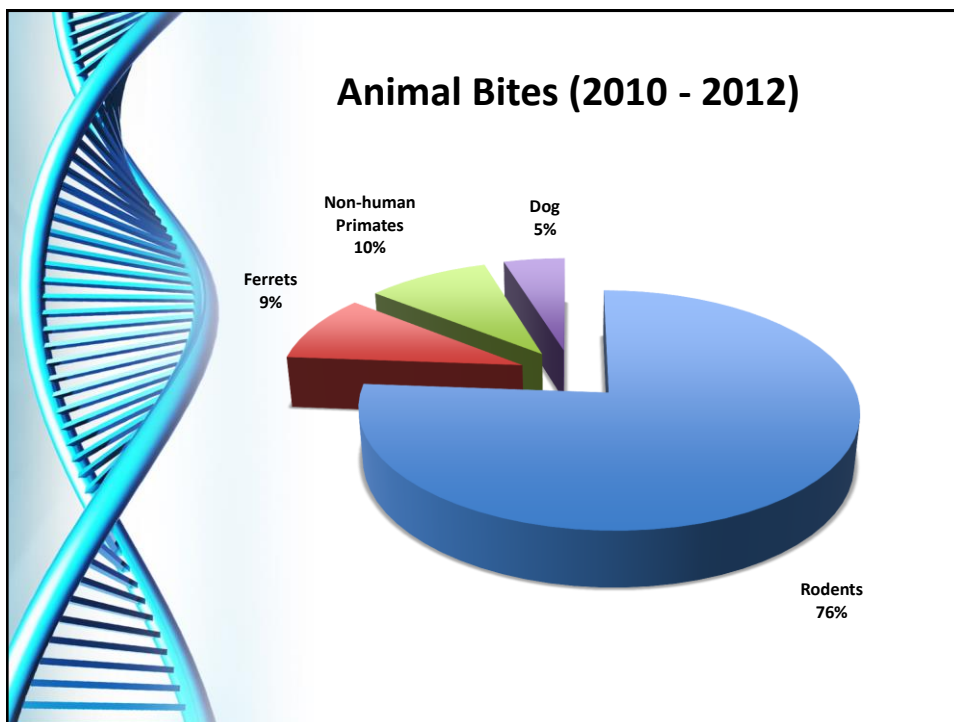
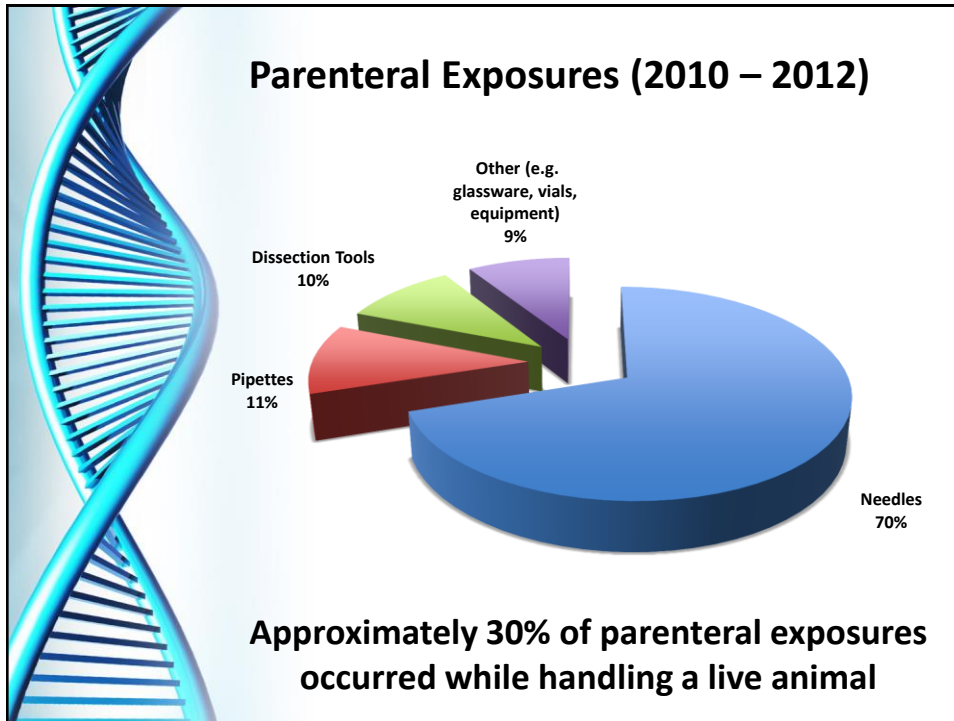
Attention: Incident Reports  
NIH Office of Biotechnology Activities  
6705 Rockledge Drive, Suite 750  
Bethesda, Maryland 20892-7985  
(For all non-USPS deliveries use Zip Code 20817)  
Telephone 301-496-9838  
Fax 301-496-9839  
E-mail: [oba@od.nih.gov](mailto:oba@od.nih.gov)

[http://oba.od.nih.gov/oba/ibc/FAQs/FAQs\\_about\\_Incident\\_Reporting.pdf](http://oba.od.nih.gov/oba/ibc/FAQs/FAQs_about_Incident_Reporting.pdf)









## ***Mustela putorius furo (Jack 'n' Jill)***




### **We know you know.... But...**

- Ensure proper PPE use at all times, ESPECIALLY EYEWEAR
- Legs and feet should be covered
- Ensure proper posting of signage for potential hazards, SOPs, and emergency response procedures
- Be constantly aware of all types of experiments being conducted, whether they have been approved, and whether they are being conducted at the appropriate containment level








## We know you know ... But ...

### Common Sharps Sense – Top 10

1. Conduct frequent training on proper sharps use and disposal.
2. Pay special attention when using sharps, avoid recapping needles
3. Empty sharps disposal containers regularly. Don't compact with hands or try to overstuff when full.
4. Don't place sharps disposal containers next to regular trash cans.
5. Don't "retrieve" items from sharps containers.
6. Ensure animals are properly restrained or anesthetized before attempting an injection.
7. Use plastic rather than glass, or sharps with built in safety features when possible
8. Inspect glassware carefully before use.
9. Tidy up breakages and equipment.
10. Avoid multiple researchers working in close proximity with sharps if possible.



## We know you know ... But...


- Make sure THEY know
  - ❑ Training ...training ... and more training
  - ❑ Provide specific examples of what can go/has gone wrong
  - ❑ Stress importance of reporting and requirements to do so (and that it's not punitive)



**IBC Self-Assessment Tool**

NIH National Institutes of Health  
Office of Biotechnology Activities

**Institutional Biosafety Committee  
Self-Assessment Tool**



[May 2013]

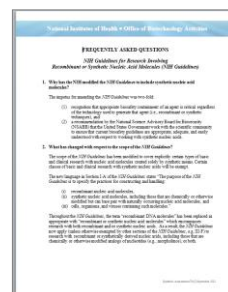
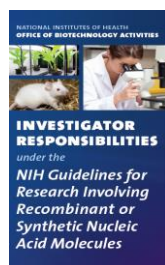
**Available online at:**  
[http://oba.od.nih.gov/rdna\\_ibc/ibc\\_training.html](http://oba.od.nih.gov/rdna_ibc/ibc_training.html)

# IBC Self-Assessment Tool

Question Number	NIH Guidelines Citation	Question	OBA Comments	Institution Comments/Notes
<b>IBC MEMBERSHIP</b>				
1	IV-B-2-a-(1)	How many members are currently on the institution's IBC?	The institution's IBC must be composed of no fewer than five members who collectively have experience and expertise in recombinant or synthetic nucleic acid molecule technology, the capability to assess the safety of research with recombinant or synthetic nucleic acid molecules, and the ability to identify any potential risk to public health or the environment. At least two of these individuals must be not be affiliated with the institution except for their membership on the IBC.	
2	IV-B-2-a-(3)	Has the institution designated an IBC Chair?	The institution must file an annual report with OBA which includes a roster of all members of the IBC and clearly indicates who is serving as the IBC Chair.	
3	IV-B-2-a-(1)	Has the institution designated a BSO on the IBC (if necessary)?	A BSO must be appointed to the IBC if the institution conducts research at BL3, BL4, or conducts Large Scale research (as defined as research in which a single containment vessel has greater than 10 liters of volume). When required, the individual serving as the BSO should be indicated on the roster registered with NIH OBA.	

1

## Updated/New Educational Materials



Please request copies!

## New Web Site



<http://osp.od.nih.gov/office-biotechnology-activities/oba/index.html>

## OBA NEWS Listserv

Subscribe to OBA\_NEWS

Send an email to:

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Suite 750  
6705 Rockledge Drive,  
Bethesda, MD 20892-7985

Phone (301) 496-9838  
Fax (301) 496-9839



**Web:** <http://osp.od.nih.gov/office-biotechnology-activities/oba/index.html>



**Email:** [oba-osp@od.nih.gov](mailto:oba-osp@od.nih.gov)

## Questions

