



SAFETY AND COMPLIANCE ALERT

UW-Madison's Institutional Biosafety Committee (IBC) and Office of Biological Safety (OBS) are charged with the responsibility to evaluate biological research on the UW campus. Risk assessments of biosafety protocols ensure that safety and compliance standards are met.

It is the responsibility of the Principal Investigator to be fully cognizant of the NIH Guidelines and its requirements. Non-compliance with or violating the NIH Guidelines can result in suspension or termination of NIH funding not just for the investigator, but for our entire institution. To facilitate a clear understanding, the IBC and OBS will undertake an education initiative and begin to send Safety and Compliance Alerts to assist UW researchers in meeting their obligations.

The following alert clarifies issues related to antibiotic resistant genes. We ask you to carefully review the alert and the accompanying NIH FAQ sheet which provides detailed information about Major Action experiments, how to request NIH/RAC and IBC review, and useful references regarding treatment options (http://oba.od.nih.gov/oba/IBC/MAJOR_ACTION_FAQS_MARCH_2008.pdf).

Compromising Treatment by Introduction of Antibiotic Drug Resistance Genes

Safety Considerations

The use of antibiotic resistance genes as selectable markers is a common and valuable tool in molecular biology. Introducing antibiotic resistance genes in disease-causing organisms, whether infectious to humans, animals, or plants, raises concerns that must be weighed very carefully. A thorough literature review will assist in determining whether the gene confers resistance to an antibiotic that might be used to treat the disease caused by the pathogen. Risk assessments must consider the following important criteria:

1. Could introduction of resistance to the drug compromise the treatment of disease? Factors that need to be considered include:
 - Potential compromise of second line treatments in addition to first line treatments
 - Potential compromise of treatment for special populations such as children and pregnant women
 - Whether expression of the antibiotic resistance gene can confer resistance to related antibiotics that are used for disease treatment
 - Potential compromise of treatments used in other countries, not just ones used in the United States
 - Potential compromise of treatments used for animals and in agriculture, not just those used for humans
 - Potential compromise of treatments used for infections that occur through routes of transmission other than the common routes (e.g., needlesticks when the common route is ingestion).
2. Are alternative approaches to doing the work available that do not confer resistance?



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3. What biological and physical containment methods (including disinfection) are used to ensure that viable organisms containing antibiotic resistance genes are not released into the environment? Bacteria (including BSL-1 organisms) can readily exchange genes including antibiotic resistance genes between different strains, species, and genera by several naturally occurring mechanisms.

Caution is advised with regard to precedents. Just because another research group has introduced a certain drug-resistance trait does not necessarily support the conclusion that it is acceptable from either a safety or compliance standpoint.

Compliance Considerations

The regulations on deliberate transfer of non-naturally acquired antibiotic drug resistance that could compromise treatment are described in Section III-A of the NIH Guidelines for Research Involving Recombinant DNA Molecules (http://oba.od.nih.gov/rdna/nih_guidelines_oba.html). Such experiments are considered MAJOR ACTIONS subject to review by the Recombinant DNA Advisory Committee (RAC) and approval by the NIH Director in addition to review by the UW-Madison Institutional Biosafety Committee, and CANNOT be initiated until NIH and UW-IBC approval is granted. It is considered a Major Action Violation of the NIH Guidelines to initiate such a project without approval with serious regulatory consequences that can be even more severe if the organism involved is a Select Agent. NIH Approval is restricted to the PI/lab that was granted approval, and specific containment conditions and other safety requirements will be stipulated prior to initiation of the work.

Finally, it is imperative that all research personnel receive training with regard to deliberate introduction of drug resistance traits. Failure to thoroughly assess the impacts and follow through on all aspects of the review process may place the research program and the UW in a non-compliant situation. Even more importantly, it may put researchers and the community at risk of exposure to a pathogen for which standard treatment is no longer available. Be sure to contact OBS staff (263-2037) if you have any questions about this important topic.