Frequently Asked Questions Concerning Risk Assessment and Containment

What resources are available which provide general information about conducting risk assessments and determining containment?

The NIH Guidelines for Research Involving Recombinant DNA Molecules Section II Safety Considerations describes the risk assessment process, criteria for Risk Group assignment and containment. More specific information is contained in the following appendices:

- Appendix B - Table 1: Basis for the Classification of Biohazardous Agents by Risk Group (RG)
- Appendix G - Physical Containment
- Appendix I - Biological Containment
- Appendix K - Physical Containment for Large Scale Uses of Organisms Containing Recombinant DNA Molecules
- Appendix Q - Physical and Biological Containment for Recombinant DNA Research Involving Animals

Biosafety in Microbiological and Biomedical Laboratories (BMBL), which is jointly published by the NIH and CDC, provides a code of practice that describes standard and special laboratory practices, equipment and facilities. It also provides information on biosafety principles, risk assessment, biosafety level criteria, and summary statements regarding wild type infectious agents.

The World Health Organization (WHO) recently published the third edition of the Laboratory Biosafety Manual.

At the safety symposium, a presentation on risk assessment and containment was given by Dr. E. Barkley. The presentation web cast and slides are available here.

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What is the definition of BSL3+ containment?

Unlike BSL2+ containment, BSL3+ is not defined in the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) or Biosafety in Microbiological and Biomedical Laboratories (BMBL). While BSL3+ is a commonly used term, only BSL3 containment is described in the NIH Guidelines and BMBL. Depending on the nature of the research, IBCs may recommend BSL3 containment with appropriate enhancements (e.g., BL3 with respiratory protection, HEPA filtration, shower out, etc.).

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What is BSL3-Ag containment?

The USDA Agricultural Research Service (ARS) defines BSL-3Ag in section 9.4.4 of the ARS CSREES ERS NASS Manual. BSL-3Ag facilities include.the containment features of BSL3 facilities, and are specifically designed to protect the environment by also including almost all of the features used for BSL-4 facilities as enhancements. All BSL-3Ag containment spaces must be designed, constructed and certified by the USDA as primary containment barriers.

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What biosafety levels of containment do the NIH Guidelines and BMBL recommend for research with influenza viruses and SARS-CoV?

In Appendix B, Classification of Human Etiologic Agents on Basis of Hazard, of the NIH Guidelines, influenza viruses types A, B, and C, as well as corona viruses, are classified as Risk Group 2 agents. The influenza agent summary statement of the BMBL recommends BSL2 containment; however, this summary statement is currently being revised for inclusion in the 5 th edition of the BMBL.The revised edition of the BMBL is expected to be published in Summer 2005. The revised influenza summary statement will initially be published in the Morbidity and Mortality Weekly Report (MMWR) available on the CDC web site and will be included with the information on this web site.

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What guidance is available for research with highly pathogenic avian influenza (HPAI)?

The CDC provides updates that include containment information for laboratory work with wild type HPAI. The WHO has developed biosafety guidelines and risk assessment information for vaccine research. Information is also available from the health agencies of other countries such as Health Canada and the United Kingdom Health and Safety Executive.

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What are the USDA regulations that must be considered when working with HPAI?

Work with HPAI requires a permit from the USDA. At the safety symposium, Dr. LeeAnn Thomas of USDA presented the permitting requirements under 9 CFR 122. She defined low and highly pathogenic avian influenza and the respective permit applications and laboratory inspections.

HPAI are also select agents. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 requires the United States Department of Health and Human Services (HHS) and the United States Department of Agriculture (USDA) to establish regulations regarding the possession, use, and transfer of select biological agents and toxins. In accordance with the Act, the USDA published new regulations in the Federal Register on December 13, 2002 (67 FR 76908-76938). The USDA regulations are set out in 7 CFR Part 331 and 9 CFR Part 121.

The regulations in 42 CFR Part 73 and 9 CFR Part 121 establish a procedure by which an attenuated strain of a select biological agent or toxin that does not pose a severe threat to public health and safety, animal health, or animal products may be.excluded from the list of select biological agents and toxins. Several recombinant reference vaccine strains of HPAI subtypes have been excluded based on results from in-vitro and in-vivo studies indicating that these strains were not pathogenic in avian species. The data requirements necessary for

exclusion consideration are available here.

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What biosafety guidance is available for research with SARS-CoV?

The WHO has published biosafety guidelines including containment recommendations for handling clinical specimens and for post-outbreak laboratory work with wild type SARS-CoV. The WHO also provides public health management information. The UK Health and Safety Executive has also developed advice.

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What factors should be considered in a risk assessment of recombinant research with pathogenic viruses?

NIH Guidelines Section II-A-3. Comprehensive Risk Assessment states, In deciding on the appropriate containment for an experiment, the initial risk assessment from Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard, should be followed by a thorough consideration of the agent itself and how it is to be manipulated. Factors to be considered in determining the level of containment include

- agent factors, such as:
  - virulence,
  - pathogenicity,
  - infectious dose,
  - environmental stability,
  - route of spread,
  - communicability,
  - operations,
  - quantity,
  - availability of vaccine or treatment,
- and gene product effects, such as:
  - toxicity,
  - physiological activity,
  - and allergenicity.

Section II-A-3 also states, Any strain that is known to be more hazardous than the parent (wild-type) strain should be considered for handling at a higher containment level. Certain attenuated strains or strains that have been demonstrated to have irreversibly lost know virulence factors may qualify for a reduction of the containment level compared to the Risk Group assigned to the parent strain.

At the safety symposium, the panel developed a set of template examples that may be helpful to IBCs when conducting a risk assessment. The first template is based on the agent, gene modification, and manipulation factors described in the NIH Guidelines. Two influenza virus research templates were developed. One template includes a hypothetical example of possible containment levels assigned to research with different recombinant influenza viruses. The other template provides a hypothetical example of possible containment levels assigned to research with different recombinant influenza viruses. This template is intended as an example of a possible approach to risk assessment. It does not represent containment recommendations made by the NIH RAC or any IBC. The template for corona viruses demonstrates that different factors and multiple systems for generating recombinant viruses need to be considered for risk assessment of SARS-CoV research.

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What biosafety levels of containment are currently being used for recombinant research with 1918 influenza viruses, highly pathogenic avian influenza viruses, and SARS-CoV?

At the safety symposium, several investigators presented current research and provided examples of risk assessments performed to determine containment for this type of research. A webcast of the presentations at the safety symposium is available here. Dr. Y. Kawaoka presented research with HPAI and 1918 influenza virus, Dr. A. Garcia-Sastre on 1918 influenza virus, Drs. R. Webster and K. Subbarao on HPAI, and Dr. R. Baric on SARS-CoV research.

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What occupational medicine issues should be considered with this type of research?

Occupational medicine services and surveillance were discussed at the safety symposium using an outline developed by Dr. J. Schmitt, OMS, NIH.

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How can an IBC review research in a new field or with an emerging virus if the IBC members do not have sufficient expertise?

When necessary for specific reviews, IBCs should augment the expertise of the committee members by consulting with ad hoc experts who can provide the appropriate expertise in the form of a written review. It was suggested at the safety symposium that possibly the American Biological Safety Association (ABSA) or scientific societies would be interested in facilitating the exchange of information among their members with experience in this research.

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