

CHAPTER 6

RISK ASSESSMENT

"Risk" implies the probability that harm, injury, or disease will occur. In the context of the microbiological and biomedical laboratories, the assessment of risk focuses primarily on the prevention of laboratory-associated infections. When addressing laboratory activities involving infectious or potentially infectious material, risk assessment is a critical and productive exercise. It helps to assign the biosafety levels (facilities, equipment, and practices) that reduce the worker's and the environment's risk of exposure to an agent to an absolute minimum. The intent of this section is to provide guidance and to establish a framework for selecting the appropriate biosafety level.

Risk assessment can be qualitative or quantitative. In the presence of known hazards (e.g., residual levels of formaldehyde gas after a laboratory decontamination), quantitative assessments can be done. But in many cases, quantitative data will be incomplete or even absent (e.g., investigation of an unknown agent or receipt of an unlabeled sample). Types, subtypes, and variants of infectious agents involving different or unusual vectors, the difficulty of assays to measure an agent's amplification potential, and the unique considerations of genetic recombinants are but a few of the challenges to the safe conduct of laboratory work. In the face of such complexity, meaningful quantitative sampling methods are frequently unavailable. Therefore, the process of doing a risk assessment for work with biohazardous materials cannot depend on a prescribed algorithm.

The laboratory director or principal investigator is responsible for assessing risks in order to set the biosafety level for the work. This should be done in close collaboration with the Institutional Biosafety Committee (and/or other biosafety professionals as needed) to ensure compliance with established guidelines and regulations.

In performing a qualitative risk assessment, all the risk factors are first identified and explored. There may be related information available, such as this manual, the NIH Recombinant DNA Guidelines, the Canadian Laboratory Biosafety Guidelines, or the WHO Biosafety Guidelines. In some cases, one must rely on other sources of information such as field data from subject matter experts. This information is interpreted for its tendency to raise or lower the risk of laboratory-acquired infection.⁽¹⁾

The challenge of risk assessment lies in those cases where complete information on these factors is unavailable. A conservative approach is generally advisable when insufficient information forces subjective judgement. Universal precautions are always advisable.

The factors of interest in a risk assessment include:

- The *pathogenicity* of the infectious or suspected infectious agent, including disease incidence and severity (i.e., mild morbidity versus high mortality, acute versus chronic disease). The more severe the potentially acquired disease, the higher the risk. For

example, *staphylococcus aureus* only rarely causes a severe or life threatening disease in a laboratory situation and is relegated to BSL-2. Viruses such as Ebola, Marburg, and Lassa fever, which cause diseases with high mortality rates and for which there are no vaccines or treatment, are worked with at BSL-4. However, disease severity needs to be tempered by other factors. Work with human immunodeficiency virus (HIV) and hepatitis B virus is also done at BSL-2, although they can cause potentially lethal disease. But they are not transmitted by the aerosol route, the incidence of laboratory-acquired infection is extremely low for HIV, and an effective vaccine is available for hepatitis B .

- The *route of transmission* (e.g., parenteral, airborne, or by ingestion) of newly isolated agents may not be definitively established. Agents that can be transmitted by the aerosol route have caused most laboratory infections. It is wise, when planning work with a relatively uncharacterized agent with an uncertain mode of transmission, to consider the *potential for aerosol transmission*. The greater the aerosol potential, the higher the risk.
- *Agent stability* is a consideration that involves not only aerosol infectivity (e.g., from spore-forming bacteria), but also the agent's ability to survive over time in the environment. Factors such as desiccation, exposure to sunlight or ultraviolet light, or exposure to chemical disinfectants must be considered.
- The *infectious dose* of the agent is another factor to consider. Infectious dose can vary from one to hundreds of thousands of units. The complex nature of the interaction of microorganisms and the host presents a significant challenge even to the healthiest immunized laboratory worker, and may pose a serious risk to those with lesser resistance. The laboratory worker's *immune status* is directly related to his/her susceptibility to disease when working with an infectious agent.
- The *concentration* (number of infectious organisms per unit volume) will be important in determining the risk. Such a determination will include consideration of the milieu containing the organism (e.g., solid tissue, viscous blood or sputum, or liquid medium) and the laboratory activity planned (e.g., agent amplification, sonication, or centrifugation). The volume of concentrated material being handled is also important. In most instances, the risk factors increase as the working volume of high-titered microorganisms increases, since additional handling of the materials is often required.
- The *origin* of the potentially infectious material is also critical in doing a risk assessment. "Origin" may refer to geographic location (e.g., domestic or foreign); host (e.g., infected or uninfected human or animal); or nature of source (potential zoonotic or associated with a disease outbreak). From another perspective, this factor can also consider the potential of agents to endanger American livestock and poultry.
- The *availability of data from animal studies*, in the absence of human data, may provide useful information in a risk assessment. Information about pathogenicity, infectivity, and route of transmission in animals may provide valuable clues. Caution must always

be exercised, however, in translating infectivity data from one species of animal to another species.

- The established *availability of an effective prophylaxis* or therapeutic intervention is another essential factor to be considered. The most common form of prophylaxis is immunization with an effective vaccine. Risk assessment includes determining the availability of effective immunizations. In some instances, immunization may affect the biosafety level (e.g., the BSL-4 Junin virus can be worked on at BSL-3 by an immunized worker). Immunization may also be passive (e.g., the use of serum immunoglobulin in HBV exposures). However important, immunization only serves as an additional layer of protection beyond engineering controls, proper practices and procedures, and the use of personal protective equipment. Occasionally, immunization or therapeutic intervention (antibiotic or antiviral therapy) may be particularly important in field conditions. The offer of immunizations is part of risk management.
- *Medical surveillance* ensures that the safeguards decided upon in fact produce the expected health outcomes. Medical surveillance is part of risk management. It may include serum banking, monitoring employee health status, and participating in post-exposure management.

Risk assessment must also include an evaluation of the *experience and skill level of at-risk personnel* such as laboratorians and maintenance, housekeeping, and animal care personnel (see Section III). Additional education may be necessary to ensure the safety of persons working at each biosafety level. The infectious agents whose risk is evaluated often will fall into the following discrete categories.

Materials containing known infectious agents

The characteristics of most known infectious agents have been well identified. Information useful to risk assessment can be obtained from laboratory investigations, disease surveillance, and epidemiological studies. Infectious agents known to have caused laboratory-associated infections are included in this volume's agent summary statements (see Section VII). Other sources include the American Public Health Association's manual, *Control of Communicable Diseases*.⁽²⁾ Literature reviews on laboratory acquired infections also may be helpful.⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁶⁾⁽⁷⁾⁽⁸⁾

Materials containing unknown infectious agents

The challenge here is to establish the most appropriate biosafety level with the limited information available. Often these are clinical specimens. Some questions that may help in this risk assessment include:

1. Why is an infectious agent suspected?

2. What epidemiological data are available? What route of transmission is indicated? What is the morbidity or mortality rate associated with the agent?
3. What medical data are available?

The responses to these questions may identify the agent or a surrogate agent whose existing agent summary statement can be used to determine a biosafety level. In the absence of hard data, a conservative approach is advisable.

Materials containing recombinant DNA molecules

This category of agents includes microorganisms that have been genetically modified through recombinant DNA technologies. These technologies continue to evolve rapidly. Experimental procedures designed to derive novel recombinant viruses, bacteria, yeast, and other microorganisms have become commonplace in recent years. It is highly likely that future applications of recombinant DNA technology will produce new hybrid viruses. The National Institutes of Health publication, *Guidelines for Research Involving Recombinant DNA Molecules*,⁽⁹⁾ is a key reference in establishing an appropriate biosafety level for work involving recombinant microorganisms.

In selecting an appropriate biosafety level for such work, perhaps the greatest challenge is to evaluate the potential increased biohazard associated with a particular genetic modification. In most such cases, the selection of an appropriate biosafety level begins by establishing the classification of the non-modified virus. Among the recombinant viruses now routinely developed are adenoviruses, alphaviruses, retroviruses, vaccinia viruses, herpesviruses, and others designed to express heterologous gene products. However, the nature of the genetic modification and the quantity of virus must be carefully considered when selecting the appropriate biosafety level for work with a recombinant virus. Among the points to consider in work with recombinant microorganisms are:

- Does the inserted gene encode a known toxin or a relatively uncharacterized toxin?
- Does the modification have the potential to alter the host range or cell tropism of the virus?
- Does the modification have the potential to increase the replication capacity of the virus?
- Does the inserted gene encode a known oncogene?
- Does the inserted gene have the potential for altering the cell cycle?
- Does the viral DNA integrate into the host genome?
- What is the probability of generating replication-competent viruses?

This list of questions is not meant to be inclusive. Rather, it serves as an example of the information needed to judge whether a higher biosafety level is needed in work with genetically modified microorganisms. Since in many cases the answers to the above questions will not be definitive, it is important that the organization have a properly

constituted and informed Institutional Biosafety Committee, as outlined in the NIH guidelines, to evaluate the risk assessment

Materials that may or may not contain unknown infectious agents

In the absence of information that suggests an infectious agent, universal precautions are indicated.

Animal studies

Laboratory studies involving animals may present many different kinds of physical, environmental, and biological hazards. The specific hazards present in any particular animal facility are unique, varying according to the species involved and the nature of the research activity. The risk assessment for biological hazard should particularly focus on the animal facility's potential for increased exposure, both to human pathogens and to zoonotic agents.

The animals themselves can introduce new biological hazards to the facility. Latent infections are most common in field-captured animals or in animals coming from unscreened herds. For example, monkey b-virus presents a latent risk to individuals who handle macaques. The animal routes of transmission must also be considered in the risk assessment. Animals that shed virus through respiratory dissemination or dissemination in urine or feces are far more hazardous than those that do not. Animal handlers in research facilities working on infectious agents have a greater risk of exposure from the animals' aerosols, bites, and scratches. Section IV describes the practices and facilities applicable to work on animals infected with agents assigned to corresponding Biosafety Levels 1-4.¹

Other applications

The described risk assessment process is also applicable to laboratory operations other than those involving the use of primary agents of human disease. It is true that microbiological studies of animal host-specific pathogens, soil, water, food, feeds, and other natural or manufactured materials, pose comparatively lower risks for the laboratory worker. Nonetheless, microbiologists and other scientists working with such materials may find the practices, containment equipment, and facility recommendations described in this publication of value in developing operational standards to meet their own assessed needs.

Other Resources

- NIH Guidelines for Recombinant DNA Molecules: <http://www.NIH.gov/od/orda/toc.html>
- NIH Office of Recombinant DNA Activities: <http://www.NIH.gov/od/orda>

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