Comparative Medicine
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Vol 67, No 3
June 2017
Pages 192-202

Overview

Institutional Oversight of Occupational Health and Safety for Research Programs Involving Biohazards

Melissa C Dyson,[1,*] Calvin B Carpenter,[2] and Lesley A Colby[3]

Research with hazardous biologic materials (biohazards) is essential to the progress of medicine and science. The field of microbiology has rapidly advanced over the years, partially due to the development of new scientific methods such as recombinant DNA technology, synthetic biology, viral vectors, and the use of genetically modified animals. This research poses a potential risk to personnel as well as the public and the environment. Institutions must have appropriate oversight and take appropriate steps to mitigate the risks of working with these biologic hazards. This article will review responsibilities for institutional oversight of occupational health and safety for research involving biologic hazards.

Abbreviation: IBC, institutional biosafety committee

Since the discovery of microorganisms and their early demonstration as the causative agents of disease, researchers have been studying microbial diseases and developing countermeasures against the organisms. As early as 1880, Louis Pasteur developed a method of attenuating virulent pathogens so they could be used to immunize animals and protect them from disease. The field of microbiology has advanced vastly over the years, in part due to the use of genetically modified animals as well as the development of new scientific methods, including recombinant DNA technology, synthetic biology, viral vectors, and xenotransplantation. Work with infectious agents involves risk; institutions must have appropriate oversight and take appropriate steps to mitigate those risks. It is incumbent upon institutions to develop appropriate biosafety and biocontainment practices and procedures to protect laboratory workers, public health, animal and plant health, agriculture, and the environment[41].

According to the Occupational Safety and Health Administration, employers are responsible for providing safe and healthy working conditions for their employees.[21] Development of an occupational health and safety program requires knowledge of the hazards present and understanding of their relative risk to occupational injury and illness. Protecting the health and safety of employees engaged in the research or involved with research animals is a joint and collaborative effort that requires the active participation of institutional management, research staff who plan and carry out research, animal care and use program managers, health and safety professionals. In addition, individual employees share the responsibility both for their own health and safety and for the health and safety of those around them.[18]

Received: 13 Oct 2016. Revision requested: 29 Nov 2016. Accepted: 05 Feb 2017.
[1]Unit for Laboratory Animal Medicine, University of Michigan, Ann Arbor, Michigan; [2]Animal Resources, Alcon Research and Development, Fort Worth, Texas; and [3]Department of Comparative Medicine, University of Washington, Seattle, Washington.
**Corresponding author. Email: mcdyson@umich.edu*

The NIH is a major financial supporter of infectious disease research. In 2015 the National Institute for Allergy and Infectious Diseases awarded more than $2.7 billion in grants for infectious disease research, with study topics varying from the basic science of disease mechanisms to clinical trials. Infectious disease research may involve the actual infectious agent, surrogate agents, and a variety of in vitro and in vivo models. Work with 'select agents'—infectious agents and toxins with the potential to pose a severe threat to public health and safety, to animal or plant health, or to animal or plant products—is a smaller yet very important subset of research with infectious agents. Their use is overseen by specific governmental regulation (7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73).[36-38] Work with infectious agents or animals exposed to them has several inherent risks that should be considered to protect the employee and the environment.

Because the focus of this overview is infectious hazards intentionally used as part of research programs, the content will not detail concerns with infectious or biologic hazards (biohazards) that are naturally or incidentally present in experimental models. Research methodologies such as xenotransplantation that can transfer pathogens to transplant recipients, work with human cell lines that can carry blood-borne pathogens, and even work with animals that can carry zoonotic diseases all represent potential sources of occupational health concern. These risks should be assessed and managed as part of the same occupational health and safety program as that for the intentional experimental use of infectious biologic materials.

Recombinant DNA and Synthetic Nucleic Acid Molecules

In 1972, researchers published details regarding the first intentional creation of recombinant DNA molecules.[2] Recombinant DNA technology entails fusing DNA material from different organisms and inserting the hybrid DNA into a host cell for repli-

cation. From the beginning, several leading researchers favored the delay of further investigation pending better understanding of the potential associated biohazards, including cancer-causing potential of laboratory-altered viruses.[33] The concerns raised by the scientific community led to the development in 1975 of the *NIH Guidelines for Research Involving Recombinant DNA Molecules*. These guidelines established the institutional biosafety committee (IBC), which provides review and oversight of research using recombinant or synthetic techniques and outlines the framework for researchers to follow when designing gene therapy experiments.[9]

The guidelines were later changed to include synthetic nucleic acid and is now known as the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (referred to as *NIH Guidelines* hereafter).[16] Synthetic biology, a new and emerging field that encompasses science and engineering, has the potential to affect many areas of society. Synthetic biologists use artificial molecules to reproduce emergent behavior from natural biology, with the goal of creating artificial life or creating interchangeable biologic parts to assemble them into devices and systems that function in a manner not found in nature.[30]

Recombinant DNA technology has been used to manipulate genes to attenuate organisms for vaccines and for research purposes. Although these new technologies have demonstrated great benefit, they also have the potential of creating hazards and present dilemmas regarding working safely with the technologies and their resultant products. In addition, manipulation of an organism's genetics may increase its virulence. One of the early examples of genetic manipulation leading to an inadvertent increase in the virulence of the organism is the insertion of the gene for IL4 into the mousepox virus. The researchers discovered that the altered virus could kill both naturally resistant mouse strains and vaccinated mice.[13] The cited study is an example of gain-of-function research, in which an organism acquires a new or enhanced biologic function. This type of research represents potential for great advancement in the understanding and treatment of infectious disease as well as great risk if the virulence and responsiveness to treatment of an organism is altered. An unintended consequence of gain-of-function research is the potential hazard it poses to personnel working with the manipulated organism. Normal safeguards, such as vaccines, may not be effective against the modified organisms. In most cases, recombinant organisms can be handled at the same biosafety level as the wild-type recipient, whereas poorly defined DNA sequences from donor organisms that might increase the virulence of the recipient organism should be handled at higher biosafety levels.[16]

Viral Vectors

Recombinant DNA technology is used in combination with viral vectors for gene therapy. Viral vectors are a key component of gene therapy because they are an effective means of transferring genes to modify specific cell types or tissues and can be manipulated to express therapeutic genes. Viral vectors include adenoviruses, retroviruses, poxviruses, adeno-associated viruses, baculoviruses, and herpes simplex viruses. The choice of virus depends on a number of factors, including the efficiency of transgene expression, ease of production, safety, toxicity, and stability.[43] Ideal virus-based vectors for most gene-therapy applications harness the viral infection pathway but avoid the subsequent expression of viral genes that leads to replication and toxicity.[34] Using the specialized molecular mechanisms of the virus has been shown to be an efficient method to transport the desired genetic material inside the cells they infect. However, early researchers did not fully appreciate the potential hazards associated with the use of viral vectors. For example, in 1999, a gene therapy trial participant developed a severe reaction to a recombinant adenovirus vector and died 4 d later.[25] Risks also are associated with the transgene itself: in 2002 several children with severe combined immunodeficiency disease enrolled in a gene therapy clinical trial developed a leukemia-like condition due to genomic integration of the vector near an oncogene promoter.[5,8] Since that time, effort and research have gone into understanding the potential hazards of gene therapy, and vectors with improved efficiency, specificity, and safety have been developed.

Regulations and Guidance Regarding Occupational Health and Safety in the Use of Biohazards

Some of the major references available when preparing an occupational health and safety program for biohazards include: *Biosafety in Microbiologic and Biomedical Laboratories*,[40] *Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules*,[16] and the *Laboratory Biosafety Manual*,[43] a globally developed biosafety guideline published by the World Health Organization. These are excellent resources for risk-based analysis that assign organisms to risk groups based on the organism's potential effect on an individual or the environment. Based on the risk classification, the resources provide recommendations on effective measures to mitigate the risk. General occupational health and safety considerations, as they relate to common infectious agents, can be found in the joint CDC–NIH publication *Biosafety in Microbiologic and Biomedical Laboratories*.[40] However that publication does not cover all infectious agents, such as new or emerging pathogens, genetically modified organisms, or recombinant organisms. Separate regulations cover the utilization of select agents (7 CFR Part 331, 9 CFR Part 121, 42 CFR Part 73).[36-38]

General occupational health and safety information directly applicable to animal-based research can be found in the *Guide for the Care and Use of Laboratory Animals*[12] and the National Research Council's publication *Occupational Health and Safety in the Care and Use of Research Animals*.[18]

Several excellent national and international organizations provide guidelines that offer additional recommendations for biosafety in animal facilities. The American Biologic Safety Organization (ABSA.org) was founded in 1984 to promote biosafety as a scientific discipline and to serve the growing needs of biosafety professionals throughout the world. The organization promotes biosafety through conferences, publications, training, certification, and voluntary accreditation. The Public Health Agency of Canada and the Canadian Food Inspection Agency monitor and verify the ongoing compliance of regulated facilities licensed for controlled activities with human pathogens and toxins or importing or transferring terrestrial animal pathogens; they also publish the *Canadian Biosafety Standard*.[24] The recently formed International Federation of Biosafety Associations (internationalbiosafety.org) promotes its mission of "safe, secure, and responsible work with biological materials" through meetings, guidelines, and certification. The international organization AAALAC (AAALAC.org) provides independent, voluntary accreditation of an institution's

animal care and use program and uses many of the mentioned references as resources in the accreditation process. A necessary component of accreditation is an acceptable and institutionally supported occupational health and safety program.

Roles and Responsibilities in an Occupational Health and Safety Program

An effective occupational health and safety program requires a number of effective and integrated functional areas in an institution. The 5 general functional areas include the animal care and use program, the research program, environmental health and safety, occupational health, and administration and management.[18] Good communication and interaction among the functional areas is important to ensure that biohazards are properly identified and reviewed by a group with appropriate expertise and that the necessary safeguards are in place to protect the personnel working with the hazards. The regulations and guidance summarized earlier provide a framework for institutional responsibilities for oversight of research involving biohazards and for defining the roles and responsibilities of the various groups. These roles encompass important areas of responsibility and support for a research program.

In this context, institutions are defined as any public or private entity participating in research using biologic hazards. Institutions are required to provide safe workplaces for personnel. Likewise, it is the responsibility of the institution and its employees to ensure compliance with regulatory standards. Because many different types of organizations use animals (for example, academic centers, private companies, government facilities), different organizational structures can appropriately oversee workplace safety programs in these diverse settings. Each institution should develop internal programs that assure compliance with regulatory requirements, identify and reduce workplace risks, and educate and protect personnel from illness and injury.[18] The institution is ultimately responsible for establishing policy, providing appropriate resources, and overseeing research programs; this exercise often includes establishing committees and positions with the delegated authority and responsibility for these practices. The institutional leadership must have a clear understanding of workplace safety issues, provide resources to support programs, and support institutional policies designed to ensure workplace safety. In addition, the leadership should encourage a climate of compliance and collaboration for all organizations and personnel involved in the program.

Environmental health and safety and occupational health. An occupational health and safety program includes both environmental health and safety and occupational health programs. The main concern of environmental health and safety programs for the use of biohazards is to prevent release of organisms or toxins outside of the controlled research environment and to prevent infection of personnel, the public, and the environment. The environmental health and safety program provides technical services that assist the institution in carrying out its regulatory and legal responsibilities associated with health and safety; this program involves people who have expertise in chemical safety, biologic safety, physical safety, industrial hygiene, health physics and radiation safety, engineering, environmental health, fire safety, and toxicology. Included in this activity are programs to collect, transport, and dispose of hazardous waste; manage responses to emergencies; monitor regulatory compliance; and provide training support and technical assistance. In contrast, an occupational health program functions to protect the health of employees from work-related risks. These programs involve primarily health care professionals, including physicians, occupational health nurses, and specialists to assess potential health risks and manage the care of employees who have acquired an occupational injury or illness. Because of their related functions, occupational health is often organizationally connected with the environmental health and safety activity.[18]

Institutional biosafety committee. The Institutional Biosafety Committee (IBC) is mandated by the *NIH Guidelines* to review, approve, and oversee projects involving recombinant or synthetic nucleic acid molecules conducted at or sponsored by the institution.[16] For projects using animal subjects, the IBC membership must include someone with expertise in animal research. Although the IBC is not required to oversee other types of biologic hazards research, this group or a similar safety oversight committee is usually tasked with the review and approval of work using nonrecombinant biohazards as well as select agents. In this capacity, the IBC (or other safety committee) provides the primary mechanism representing institutional oversight of biologic hazards research.

Biosafety officer. Also defined in the *NIH Guidelines* is the role of the biosafety officer for institutions using large-scale production of recombinant or synthetic nucleic acids and the use of these materials at biosafety level 3 or 4.[16] The biosafety officer is responsible for laboratory inspections, reporting of noncompliance, reporting of research related accidents or illnesses, developing emergency plans, and providing advice on laboratory security. A specific person must be designated as an institution's biosafety officer when select research is conducted (for example, recombinant DNA research requiring BL3 containment). For other research, institutions may elect to assign these responsibilities collectively to safety personnel and the environmental health and safety departments.

The principal investigator or laboratory director is the person who oversees research projects using biohazards and the laboratory personnel responsible for the work. This person should work closely with the IBC and other oversight bodies and personnel at the institution to ensure compliance with regulations and policies for the use of hazards and research. It is also important to ensure that work has been evaluated and approved before conduct, report significant problems or violations of regulations and policies, report new information and updates regarding the hazard and its use, and ensure that personnel are trained in appropriate techniques.

Animal resources programs and institutional animal care and use committees. The use of hazards in animals requires that the IBC share responsibility for some aspects of oversight with IACUC and animal resource programs. Practices for managing and overseeing the risks of hazards used in animals are often determined in collaboration between the IBC, IACUC, and animal resources program. When personnel or groups share responsibility for oversight in this manner, they must have a means to ensure that all groups are notified of relevant information. For example, the IACUC should confirm that the IBC has been notified of pertinent hazards listed in IACUC protocol applications. The IBC should confirm IACUC involvement in projects involving animals. This communication can be done through contingent ap-

provals (IBC approval contingent on IACUC approval; institution withholds release of funds to the investigative group pending both IBC and IACUC approval) or by crossover of personnel on both committees. In addition, personnel such as veterinary and animal care personnel providing support and care to research subjects must be included in oversight, health, safety, and training programs.

Clearly, oversight of research using biohazards is complex and requires the participation of many organizational bodies, programs, and personnel. Communication and clear roles and responsibilities are integral to a smoothly functioning system of oversight and for establishing a successful culture of compliance and safety at an institution.

Risk Assessment

The identification of hazards and assessment of risk are initial steps in determining the safety and security practices necessary for the use of a hazardous agent.[14] Biohazards intended to be used in research programs should initially be identified by the principal investigator and presented to appropriate institutional review entities, such as the IBC. Biohazards should be reviewed and approved prior to their use in the laboratory or animal facilities.

Assessing the risk of hazards is a key process in determining laboratory and safety practices to prevent harm to employees and ultimately the public and environment. Risk assessment is a shared responsibility at multiple levels of a research program. Assessment begins with the principal investigator's identification of the hazard and suggestions regarding safety practices and continues with review by safety professionals, animal care and use program personnel, laboratory personnel and relevant committees (for example, IACUC). Risk assessment determinations should not be viewed as static and should evolve with changes in knowledge of and experience with the agent, advances in technology, and modifications to laboratory practices and methods involving use of the agent.

Risk assessment should take into account factors directly related to the agent itself (for example, route of transmission, infectious dose, environmental stability, host range, severity of potential disease, treatments), hazards associated with laboratory procedures (for example, use of sharps, aerosolization, infection of animals that allow replication of the hazard, and animal bites or scratches), training and capability of the staff, and available equipment and facilities.[4] Genetically modified organisms are assessed in similar fashion, but it is important to also consider that the genetic modification itself may serve to increase or decrease the risks associated with the agent.[16]

Information identified by risk assessment provides a guide for the selection of appropriate biosafety levels (encompassing microbiologic practices, safety equipment, and facility safeguards), and biosecurity practices.[40] Ideally, determinations are made by evidence-based consideration of risk,[14] however data and agent-specific information may not always be available. Careful risk assessment requires a balanced approach that uses available data yet refrains from selecting safeguards that are more stringent than necessary and that might impose unnecessary burden and expense and increase the risk of noncompliance with safety standards. "However, where there is insufficient information to make a clear determination of risk, it is prudent to consider the need for additional safeguards until more data are available."[40]

Infectious agents are classified into risk groups (RG1 through 4) according to their characteristics, including capability to infect and cause disease, virulence and severity of disease, and the availability of preventative measures and treatments[40] (Figure 1). Risk groups correlate with but do not equate to biosafety levels. "A risk assessment will determine the degree of correlation between an agent's risk group classification and biosafety level."[40] Biosafety levels for work with biohazards are divided into 4 groups according to the degree of protection provided to personnel, the environment, and the community when working with hazards. These are designated BSL1 through BSL4 for laboratory-based work and ABSL1 through ABSL4 when research is conducted involving animals. Biosafety levels are thoroughly detailed in *Biosafety in Microbiologic and Biomedical Laboratories*.[40]

Exposure Control

The goal of a biosafety program is to contain biohazards used in research. Biologic risk can be reduced and controlled by the correct application of internationally recognized procedures, such as appropriate microbiologic techniques, suitable containment apparatus, adequate facilities, and protective barriers.[6] These features can only be effective when used consistently and correctly. Improper use, lack of validation, and neglecting regular reassessment can increase the risk of exposure by decreasing the level of protection provided.

When standard laboratory practices and techniques are not sufficient to obtain biohazards, additional measures are needed. As stated in *Biosafety in Microbiologic and Biomedical Laboratories*, "The most important element of containment is strict adherence to standard microbiologic practices and techniques"[40] (Figure 2).[6]

Safety equipment functions both to contain hazards and to protect personnel working with hazards. Biologic safety cabinets filter airflow while the hazard is being used within a defined work area to prevent exposure of personnel and the environment. Sealed containers can serve to minimize the risk of spills and aerosolization of hazards during storage, transport, and other laboratory practices, such as centrifuging. Personal protective equipment, such as gloves, gowns, shoe covers, respirators, and goggles, provides protection to the employee. However, appropriate training in the use of personal protective equipment, including donning, use, and doffing, are essential to the effectiveness of these products.

Secondary barriers are provided by the facility itself. Physical separation of laboratory work areas from public access, specialized ventilation systems including air-filtration systems (HEPA filtration), and even airlocks may be used to control access to or contain potential hazards.

Appropriate containment and handling of infectious waste is imperative. Waste must be correctly packaged, clearly labeled, and appropriately decontaminated prior to leaving containment areas and entering the waste stream. Autoclaving, chemical disinfection, and gaseous or vaporous disinfection are commonly used tools. These methodologies should be determined as part of the risk assessment and hazard-handling determinations.

In addition, the CDC, International Air Transport Association, and Department of Transportation have oversight of and standards for the shipping of hazardous substances, and institutions are required to follow these standards when importing or exporting materials.[11,35-38] Standards for transporting biohazards should also be determined to protect loss or spills of hazardous material during intrainstitutional transport.

	Description of risk group according to	
	NIH Guidelines for Research Involving Recombinant DNA Molecules[16]	World Health Organization's *Laboratory Biosafety Manual*[44]
Risk group 1	Agents that are not associated with disease in healthy adult humans	No or low individual and community risk: microorganism is unlikely to cause human or animal disease.
Risk group 2	Agents associated with human disease that is rarely serious and for which preventative or therapeutic interventions are *often* available	Moderate risk to individuals but low community risk: pathogens that can cause human or animal disease but are unlikely to be serious hazards to laboratory workers, the community, livestock, or the environment; laboratory exposures may cause serious infection, but effective treatment and preventative measures are available, and the risk of spread of infection is limited
Risk group 3	High risk to individuals but low community risk: agents associated with serious or lethal human disease for which preventative or therapeutic interventions *may* be available	High risk to both individuals and community: pathogens that usually cause serious human or animal disease and can be readily transmitted from one individual to another either directly or indirectly; effective treatment and preventative measures are usually available
Risk group 4	High risk to both individuals and community: agents likely to cause serious or lethal human disease for which preventative or therapeutic interventions are not *usually* available	High risk to both individuals and community: pathogens that usually cause serious human or animal disease and can be readily transmitted from one individual to another either directly or indirectly; effective treatment and preventative measures are not usually available

Figure 1. Classification of infectious microorganisms according to risk group.

Special Considerations for Research Involving Animals

Live animals can compound the risk of hazards used in research programs. Animals themselves can injure staff due to normal behavior such as scratching or biting if socialization or restraint measures are inappropriate. In addition, animals can carry zoonotic diseases inherent to their species (for example *Macacine herpesvirus* 1 [B virus], Q fever). Bites, scratches, respiratory droplets, and splash exposure to animal body fluids can increase the risk of spread of endemic or intentionally administered infectious agents. Furthermore, live animals have the potential to support the replication and spread of the organism and thus pose risk to personnel and the environment. Humanized animals, which are engrafted with functional human immune systems, have a greater potential than their wildtype conspecifics to support active infections with human pathogens. Immunocompromised animals have a higher potential than immunocompetent animals to allow replication and subsequent shedding of an infectious agent. Once infected, animals must be contained safely to prevent their escape from appropriate housing. In addition to containment of the animals, contaminated caging, food, water, bedding, wastes, and carcasses are all important considerations regarding the safe use of biohazards and must be appropriately packaged, labeled, and decontaminated before being removed from containment facilities.

Disaster Plans and Emergency Response

Even with the best trained staff and use of appropriate equipment and facilities, accidents may occur that result in a risk of personnel exposure or release of hazardous materials. Therefore, plans and processes should be established to address potential spills, accidents, natural disasters, and even acts of terrorism. Mechanisms for addressing exposures, such as failure of personal protective equipment, needle sticks, and animal bites or escapes, should be clear to staff, and reporting should be encouraged so that mistakes are acknowledged and addressed and preventative measures can be put in place to prevent future accidents. Appropriate equipment to manage spills should be available and include appropriate signage and materials to safely clean up spills without further injury. Emergency contact information should be readily accessible for personnel. Comprehensive disaster plans should be created to address disasters, such as facilities or equipment failures, fires, natural disasters such as flooding and tornadoes, and illegal or terroristic activity. Staff should know how to contact emergency services, secure hazardous materials and animals, and evacuate facilities. Drills or practice sessions can be helpful in ensuring that all responsible personnel understand their roles and the resources available to them during an emergency.

Biosecurity

In addition to safety practices that prevent exposure to and release of a hazard, security of biohazards is an important consideration. Biosecurity is described as "the protection of biohazardous or microbial agents used in research from loss, theft, diversion, or intentional misuse."[40] There are no current federal regulations for biosecurity programs for the use of biohazards except for select agents or toxins (42 CFR 73, 7 CFR 331, and 9 CFR 121).[36-38] However, it is still valuable to implement a biosecurity program for all biologic and recombinant agents. Many of the measures used in the practice of biosafety also serve as measures of biosecurity, such as assessing experience and abilities of personnel, limiting access to research materials to necessary persons only, assessing laboratory practices to ensure that materials are used prudently and safely, and establishing emergency plans.[11] Balancing the need for communication related to safety with that for clear signage and communication regarding hazards may present conflicts between biosafety and biosecurity. These polarized needs should be balanced relative to the risks of both concerns. The success of both biosafety and biosecurity programs require an institutional and laboratory culture that accepts and follows regulations and policies to ensure compliance.

Category of work practices	Recommendations
Reducing number of personnel at risk of exposure	• Restrict access to the work area • Provide warnings of hazards and advice about special requirements
Reducing exposures by direct and indirect contact	• Keep hands away from mouth, nose, eyes, and skin • Wash hands when contaminated and when work is completed • Decontaminate work surfaces before and after work and after spills of a hazardous agent • Use appropriate methods to decontaminate equipment, surfaces, and wastes • Substitute less-hazardous materials for hazardous materials whenever possible • Wear personal protection equipment (for example, gloves, gowns, eye protection)
Practices to reduce percutaneous exposure	• Eliminate the use of sharp objects whenever possible • Avoid recapping needles, and use needles with self-storing sheaths or those designed to protect the user • Keep sharp objects in view, and limit use to a single open needle at a time • Use appropriate gloves to prevent cuts and skin exposure • Select products with puncture-resistant features whenever possible • Use puncture-resistant containers for the disposal of sharps • Handle animals with care and use appropriate restraint techniques to prevent scratches and bites
Practices to reduce exposure by ingestion	• Use automatic pipetting aids; never pipette by mouth • Do not smoke, eat, or drink in work areas used for the care and use of research animals • Keep hands and contaminated items away from mouth • Protect mouth from splash and splatter hazards
Practices to reduce exposure by inhalation	• Use chemical fume hoods, biological safety cabinets, respirators, and other containment equipment to control inhalation hazards • Handle fluids carefully to avoid spills and splashes and the generation of aerosols • Use inline HEPA filters to protect the vacuum system

Figure 2. Recommended practices for occupational health and safety in research settings (adapted from reference 17, with permission). Strict adherence to safety practices in the laboratory is essential to the containment of biologic hazards . Employees should understand the hazards associated with the procedures that they are performing, recognize the routes through which they can be exposed to those hazards, select work practices that minimize exposures, and, through training and experience, acquire the discipline and skill necessary to sustain proficiency in the conduct of safe practices.

Occupational Health Care Services

Provision of occupational health care services is a key component within the larger occupational health and safety program.[18] Broadly speaking, occupational health care services encompass efforts to minimize risks to personnel (especially those most susceptible), as well as early detection and effective treatment of injuries or illnesses when they occur. For research using biologic hazards, the primary focus of an occupational health care services program is on occupationally acquired disease. Precise, minimal components of an institution's occupational health care services are not defined; rather the breadth and intensity of provided services should be consistent with the anticipated hazards and level of health risks inherent to an institution's overall research program. The overall structure and complexity of an occupational health care services program should be customized to each institution as indicated by an exposure assessment of potential health risks to personnel. As such, institutions vary greatly in the specific occupational health care services provided to their employees. However, each institution is responsible for ensuring that individual's medical records and other personal health information are adequately protected, consistent with the Health Insurance Portability and Accountability Act (HIPAA).[39]

Many issues need to be considered in designing effective and efficient occupational health care services including program administration, health surveillance programs, employee vaccination programs, and injury and illness response procedures.

Program administration. Provision of effective and efficient occupational health care services requires active collaboration of multiple individuals and groups, including institutional leaders, occupational health specialists, health care providers, animal care personnel, veterinary personnel, and environmental health and safety specialists. To be effective, each should be granted sufficient responsibility and authority by the institution to influence and support the program. Specialized consultants and researchers should be involved as subject matter experts, as needed. The educational background and dedicated time commitment of designated heath care providers (for example, physicians, nurse practitioners, physician's assistants, and nurses) will differ between institutions. Providers may be employed directly by the institution or may be contracted consultants. It is the institution's responsibility to ensure that health care providers are sufficiently qualified for their roles through prior training and experience in occupational health. In addition, health care providers should have direct knowledge and familiarity not only with the potential hazards encountered by employees but also with general employee characteristics (for example, educational background, previous experience, skill level), personnel job duties, the work environment (for example, facilities and equipment), and specific risks inherent to work with animals and approved research protocols. This knowledge and familiarity is best accomplished through regular visits to worksites, observations of job tasks, and interactions with employees and managers.

Personnel to be provided occupational health care services should be determined not strictly by job titles and classifications but rather based on a risk assessment of potential exposure. All personnel with work duties involving animals, their tissues, their environments, or their waste should be considered, including animal care personnel, research personnel, students, volunteers, building maintenance personnel, janitorial staff, security personnel, and select vendors. This population also includes visitors, volunteers, and those not employed directly by the institution (that is, contract personnel). The level of services and health protection should be consistent across groups with similar levels of risk. For contract personnel, it is the institution's responsibility to ensure that the external employer provides a comparable level of occupational health care services to their employees providing services to the institution.[42] In addition, the institution is responsible for ensuring that individuals' medical records and other personal health information are adequately protected, consistent with the Health Insurance Portability and Accountability Act.[39]

Health surveillance programs. Health surveillance programs are common components of an institution's occupational health care services. Their primary purpose is to detect workplace-acquired disease in its early stage, when a cure is still possible.[15] To be efficient and minimally intrusive to personnel, the program should be limited to the degree and variability of risks incurred by personnel. As a result, the program may be tiered to provide more comprehensive evaluation of high-risk personnel with less evaluation of those at low-risk.

Health surveillance programs often include survey-based evaluation of personnel health and work-based risk factors to identify individuals for whom medical evaluation and other interventions (for example, medical counseling, provision of accommodations) are indicated. Surveys should be clearly understandable by the user, consistent with privacy regulations, and conducted at an appropriate frequency. The institution should determine whether survey participation is required or optional for personnel, recognizing that acceptable employee participation may range from a simple acknowledgment of survey receipt to completion of an extensive questionnaire.

In addition, health surveillance programs may include required or optional medical evaluations to be conducted prior to employment; periodically at a frequency determined by hazard assessment; following an incident, concern, symptom development, or injury; and at or near employment termination.[15,31,42] If indicated by risk assessment or required work practices and safety equipment, medical evaluations may include physical exams, biologic monitoring of employees for evidence of hazard exposure, and assessment of physical ability to use select safety equipment (for example, respiratory function testing and annual fit test for use of an N95 respirator). Although the collection and storage of baseline serum samples was once common, its use is now typically reserved for a limited number of infectious agents and experimental conditions that warrant the appreciable cost and sample management programs required to reliably maintain samples over time.[17] In addition, employee health assessments function as a means to provide supplemental education specific to individual employee's job tasks and personal health conditions and to facilitate confidential conversations between employees and health care professionals.

In addition, health surveillance programs provide a means to monitor the effectiveness of an institution's occupational health and safety program including engineering controls, work practices, and safety equipment use.[15] As a result, potential improvements to worker safety may be identified. However, for health surveillance programs to serve these functions, data obtained through the program should be managed appropriately and readily accessible for comprehensive evaluations conducted at an appropriate frequency.[42] To identify trends not otherwise apparent when examining discreet data points, these evaluations should analyze data collected from each employee throughout their employment as well as across all personnel over time.

For a health surveillance program to be successful, both individual personnel and an institution's administration must trust and support the program. A culture of safety is essential throughout all levels of the institution and personnel should be assured of the program's purpose (that is, detection of workplace-acquired disease) and benefits. The institution should clearly demonstrate that its health surveillance program is not punitive to employees nor intended to separate personnel from their jobs. Personnel need to be assured that when a health issue is identified through the health surveillance program, the institution will provide necessary accommodations for them to continue in their existing positions or, if reasonable accommodations are not feasible or employee health cannot be protected, the institution will transfer the employee to an appropriate alternate position.[15]

Similarly, personnel should periodically be reminded of the importance of reporting illnesses, incidents, and 'near-misses' through the submission of incident reports, and they should be assured that such reporting does not negatively affect their employment. Each reported event should be evaluated and a job safety analysis performed, which may include the onsite evaluation of facilities, equipment, or tasks by safety personnel.

Employee vaccination programs. Unfortunately, laboratory-associated infections with organisms purposefully administered to animals do occur in animal research programs.[23,28,32] Laboratory-

associated infections are generally assumed to be underreported in part because of employee fear of embarrassment or reprisal and because of undiagnosed or asymptomatic infections. Specific animal-related procedures have been shown to generate aerosols and contamination of the environment including intranasal and parenteral inoculations and handling of contaminated bedding.[23,27,28,32] Of reported laboratory-associated infections, many have been directly attributable to known exposure events, including needle and other sharps injuries, animal bites, contact with animal ectoparasites, purposeful aerosol exposure of animals, aerosols generated during animal tissue processing, and incorrect selection or use of safety equipment.[10,22,23,26,32] Only a minority of animal-related infections are attributable to parenteral exposure; most are associated or presumed associated with aerosol exposure.[22] The risk of aerosol infection is heightened with highly pathogenic organisms or organisms with very low infectious doses. In the latter, laboratory-associated infections have occurred in personnel despite observance of required safety procedures and utilization of appropriate safety equipment.[10,14,23] Vaccination of personnel working with these agents have been associated with lower rates of laboratory-associated infections.[28,29]

An institution may elect to initiate an employee vaccination program for multiple reasons, including research protocols involving purposeful aerosol exposure of animals, to help mitigate known or unrecognized exposures to highly pathogenic organisms or organisms with very low infectious dose and to potentially decrease postexposure prophylaxis administration after low-risk or suspected exposure events with select organisms (for example, bacterial pathogens). For viral vector studies, prophylactic vaccine selection should consider when the genetic modifications of the viral vector might elicit an altered immunogenic profile that could negatively affect an individual's immunologic response to the vaccine or infection.[1] General guidance on the administration of specific vaccines and toxoids is provided by the Public Health Service Advisory Committee on Immunization Practices.[3]

Injury and illness response. Institutions are subject to multiple regional and federal regulatory requirements regarding tracking and reporting employee work-related injuries and illnesses. For instance, the Occupational Safety and Health Administration generally requires institutions with greater than 10 employees to document each recordable injury or illness case on OSHA Form 300 (*Log of Work-Related Injuries and Illnesses*) within 7 d of being notified of the case and maintain the log for at least 5 y. Institutions are then required to post an annual summary (OSHA Form 300A, *Summary of Work-Related Injuries and Illnesses*) of the preceding year's cases in a visible location in the workplace.[20]

Although injuries and illness must be handled appropriately when they occur, a primary objective of Occupational Health Care services is to prevent their occurrence. It is crucial that plans be developed prior to initiation of work with infectious agents detailing response procedures for work-related injuries, personnel exposure events, and known and suspected illnesses.[42] Plan development requires participation by people with a diverse range of expertise, including occupational health and safety personnel, environmental health and safety personnel, experienced animal resources staff and veterinary care personnel.[7] In addition to medical records and incident reporting and documentation mechanisms for occupational safety concerns (for example, OSHA 300 form), it is valuable to collaborate with institutional departments that support workers compensation and medical leave issues for employees and to provide appropriate communications and documentation regarding incidents and illness to them. Depending on the hazards (for example, select agents) and facility type (for example, secure, high-containment laboratories), the involvement of security personnel and first-responders may be indicated. Medical personnel who may attend to injured or ill employees should have a working knowledge of potential hazards, including potential routes of exposure and transmission, appropriate prophylactic exposure procedures (if applicable), symptom and illness monitoring, and available treatments.

Response plans should clearly define employee responsibilities, the order of response procedures, and the availability and appropriate use of emergency equipment. Personnel should receive continuous training on the plans. In addition, drills should be periodically conducted to ensure response plans are complete, reliable, and easily executable.

Personnel Training and Education

According to *Biosafety in Microbiologic and Biomedical Laboratories*, "the most important element of containment is strict adherence to standard microbiologic practices and techniques. Persons working with infectious agents or potentially infected materials must be aware of potential hazards, and must be trained and proficient in the practices and techniques required for handling such material safely."[40] Unfortunately, even with extensive history and understanding of risks of laboratory-associated infections, these infectious are still a threat in modern laboratories and animal facilities.[6] High-quality training programs for personnel involved in the use of biohazards in research are essential in reducing the risk of exposure and release of materials. Training should not be limited to laboratory workers but should incorporate all persons within the occupational health and safety program, including animal care and use personnel, physical plant and janitorial staff, and any volunteers or visitors that may pass through hazardous areas.

The training of laboratory staff directly involved with experiments using biohazards should involve content regarding epidemiology, pathogenicity, and human susceptibility to the biologic materials as well as instructions for direct handling of hazardous biologic agents and institutional expectations for regulatory compliance, documentation, and reporting to oversight bodies.[6] Specific regulations dictate the content and regular provision of training for personnel working with blood-borne pathogens or select agents.[19,38] These trainings require content involving risks and appropriate practices and protections for employees working with these hazards. In addition, these regulations dictate that the training is required at hire and annually thereafter. Although these requirements do not exist for all biologic hazards, they are a valuable model to consider for supporting the knowledge of risks and appropriate safety practices. In addition "engaging laboratory leadership in biosafety training activities and providing job specific training to all persons entering biocontainment laboratories are also important to safe practices and promoting a collective responsibility toward safety."[4] Health care providers, as well as at-risk personnel, should be appropriately trained to recognize clinical signs and symptoms specific to the hazards and agents to which personnel may be exposed. Adjunctive personnel including animal care and use personnel, plant and janitorial staff, and visitors and volunteers should be provided training based on

their level of risk associated with their job duties. Similar to that for laboratory staff, this training should include knowledge of the risks associated with the specific biohazards, appropriate work practices required to contain the materials and prevent exposure, and institutional regulatory and reporting expectations.

Training programs should be oriented to adult learners and tailored to the expected audience, taking into account such things as their level of understanding, previous experiences, and job duties. In addition, programs should consider the language proficiency of learners (for example, nonnative English speakers) and ensure that materials and courses are appropriate for communicating necessary information to all employees. It is vital that institutions actively support training activities and reinforce their importance.[4] As reported previously, "persons involved in laboratory accidents in laboratory accidents tend to have low opinions of safety programs, to take excessive risks, to work too fast, and to be less aware of the infectious risks of the agents they are handling."[14] Formal training should be a continuous and ongoing process, delivered throughout a person's employment. Training should not be regarded as a passive process, where information is simply transmitted from teacher to learner. From their training, personnel should acquire a firm understanding of why equipment or processes have been selected, what they are designed to do, their limitations, and the health consequences that may result if procedures are not followed or equipment is not appropriately used. Personnel should be assessed for their understanding and ability to implement training through the use, for example, of quizzes and proficiency evaluations. Assessment results should then be used to modify training and identify alternate educational opportunities. Finally, all training activities must be documented and tracked so that employers can clearly determine not only the training that an employee received but also the training that an employee lacks or needs to repeat periodically.[7]

Information Management

Along with the identification of hazards, the identification, assessment, training, and monitoring of personnel working with a hazard in the laboratory or in the animal facilities is critical to appropriate hazard containment and personnel protection. Management of this information is a critical component of the institutional support for an effective occupational health and safety program. Documentation of processes, personnel, training, and assessments are necessary to ensure required practices are occurring appropriately and to provide means for program assessment. In addition, as previously discussed, occupational health and safety programs generally involve shared responsibilities at many levels of an institution. Clearly defined roles and responsibilities of each of these areas require effective information management and sharing for successful shared oversight.

The principal investigator is primarily responsible for ensuring that laboratory personnel are appropriately trained, competent, and compliant with laboratory safety practices. However this responsibility also extends to the institution and oversight bodies that participate in the assessment and monitoring of laboratory safety practices. Often, institutional oversight bodies, including the IBC, environmental health and safety groups, and biologic safety officers, track personnel that are involved in research with biohazards through IBC and or animal care and use applications. This tracking allows the institution to confirm when employees enter the system, to control when and how they are trained in institutional policy and appropriate practices, links them to occupational health services, and documents their exit from the system (thus removing their access to hazardous materials). When the use of hazards extends into other research areas, such as those involving humans or animals, the staff supporting those areas (for example, husbandry and veterinary personnel) need to be included in the tracking and training processes and in occupational health programs to ensure their safety and their safe work practices.

To be maximally effective, an occupational health and safety program should be supported by a robust and agile information management system. At a minimum, the system should have the capability to track past and planned future activities (for example, training sessions, surveillance events), facilitate exchange of information between necessary persons (for example, medical and health and safety professionals), and permit data analysis and retention. In addition, the system should be easy to use and appropriately maintained and updated to ensure reliable, long-term use. Such information management systems may require substantial financial and technologic support from the institution.

Program Evaluation

Much of the work of hazard identification, risk assessment, training and assessment of staff, and establishing biosafety and biosecurity practices happens before research projects commence. Routine reassessments, retraining, and regular review of practices and standards are imperative practices for principal investigators and institutions to confirm that safety practices continue to be upheld and changed and improved where needed. Proposals for the use of animals and hazards have a limited lifespan and should be reevaluated on a regular basis by the institution or its delegates. Regular inspections by the oversight bodies (including IACUC and environmental health and safety) are valuable tools for auditing safety and containment practices. Inspections may include evaluation of laboratories, animal housing and use spaces, storage and processing areas, and waste management locations and their associated procedures. Reports of laboratory inspections, laboratory safety practices, facility and equipment evaluations, noncompliance, injury, new data on the handling and risks of the agents, and so forth, that should occur routinely throughout the life of a research program can be evaluated at this time to assess whether changes need to be made in the biosafety and biosecurity practices established for the research.

Occupational health and safety programs should not be regarded as static but rather as dynamic and continually evolving to best serve the needs of both the institution and its personnel. Personnel should be sufficiently empowered and supported to report safety concerns. This support is especially important for personnel at direct risk of exposure, because they are often uniquely positioned to recognize new hazards and risks and to observe the safety practices of others.[4] Each reported incident should be used as an opportunity to critically assess and potentially improve program components to avoid future incidents. In addition, both individual program components and the program as a whole should be evaluated by all involved groups at a regular, minimal frequency. The involvement of experienced personnel unfamiliar with the program or external to the institution can be especially valuable in the evaluation process by providing fresh perspectives and potentially identifying issues and efficiencies not readily apparent to internal personnel influenced by institutional history.

Conclusions

Research with hazardous biologic materials is essential to the progress of medicine and science and to increased understanding of the flora and fauna that we live among and on which we depend. However, this research can pose significant risk to personnel as well as the public and the environment. Institutions have both ethical and regulatory responsibilities to provide robust and effective occupational health and safety programs that oversee, manage, and mitigate risk. Occupational health care services programs are complicated in that they support a vast array of research and involve numerous oversight bodies and personnel. Clear roles and responsibilities and effective management are essential tools to support the successful application of an institutional occupational health and safety program. Lastly, the commitment and support of senior leadership to workplace safety is an integral component in establishing and supporting an institutional culture of compliance and safety, without which an occupational health and safety program cannot thrive.

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