

REVIEW ARTICLE



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Safety considerations for working with animal models involving human health hazards

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Abstract

A human health hazard may constitute a variety of hazards that are encountered in an animal facility. Health hazards include physical, chemical, radioactive, or biological hazards such as cage and rack washers, chemicals used for cleaning and disinfection, experimental drugs or biologics, radioactive isotopes, zoonotic diseases, allergens, experimental infectious agents, or biological toxins. This article will focus on experimental infectious agents and biological toxins (biohazards) that are hazardous to both animals and humans and require biological containment (biocontainment) to prevent their inadvertent release into the environment. Key areas for safely managing a biocontainment animal care and use program and vivarium are described. While scientific research involving health hazards has created some challenges, it has also provided some excellent advances in methods and technologies. The ideas and approaches in this article will be useful for those just entering this field of research and those who have committed their careers to the safe use of animals exposed to biohazards.

KEYWORDS

animal models, biocontainment, hazards, safety

1 | INTRODUCTION

The consequences of accidental exposure of personnel to biological hazards (biohazards) can be quite severe, including clinical disease, hospitalization, and even death. It is paramount that consideration be given to the type of biohazard and the protection of the personnel. Biohazards in the animal facility can come from many sources and it is important to take all the sources into consideration. Sources can include zoonotic diseases carried by the animal models, contaminated cell lines or other biological material; and experimental infectious agents and biological toxins. Practices and procedures should be in place to prevent the introduction of adventitious agents into the animal facility, such as purchasing specific pathogen-free animals, sentinel monitoring, and testing biological materials for infectious agents prior to use in

animals. Practices and procedures should also be in place to protect the personnel working in the animal facility, such as personal protective equipment. Besides the practices and procedures for safely working in a conventional animal facility, there should be additional safeguards in place at institutions where infectious agents are experimentally introduced into animals. The primary concepts of working in a biocontainment facility focus on the prevention of spread of the agent, protection of the personnel working in the facility, and the protection of the environment outside of the facility. To achieve these goals, the concept of assessing the risk (risk assessment); the components and practices of a biocontainment program; the variety of primary and secondary containment methods; the oversight of a biocontainment program; and the areas of occupational health and safety are described.

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2 | PROGRAMMATIC CONSIDERATIONS

2.1 | Risk assessment

The tremendous importance of risk assessment is demonstrated by its pervasiveness in nearly every current guidance publication that applies to working with biohazards or animals. The National Institutes of Health (NIH) publication, *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), contains a detailed discussion of the process and importance of conducting an effective biological risk assessment.^{1(p9)} The *Guide for the Care and Use of Laboratory Animals* (Guide) stresses the importance of risk assessment in mitigating hazards associated with the experimental use of animals, and specifically discusses the need for assessing hazards associated with animal experimentation involving hazardous agents.^{2(p18)} Since the basic components of the risk assessment process are universal, it can be applied to most situations involving the potential exposure to a hazard in the workplace. When working with biohazards, a common approach is to use an agent- and activity-based risk assessment that involves the following components: identification of the hazard; identification of the activities that can result in exposure to a hazard; the likelihood of the hazard to cause harm upon exposure; and determining the possible consequences.^{1(p16)} A risk assessment matrix is a common tool used to visualize and quantify the overall risk and is based on 2 criteria: the likelihood or the probability of the event occurring; and the consequences or the severity of the impact if the risk occurs.^{3(p1297)} When working with animals, it is critical that the additional risks the animals and related experimental activities create are factored into the risk assessment equation. The information provided by the risk assessment is then used to establish the appropriate biosafety levels and safeguards. It is important to realize that risk assessments are an ongoing process, since the risk may change during the conduct of the study.

2.2 | Animal biocontainment program

A fundamental objective of any biosafety program is the containment of potentially hazardous biological agents and toxins, and the term biocontainment is used to describe safe methods, facilities and equipment for managing infectious materials and biological toxins in the laboratory environment where they are being handled or maintained. Within an animal biocontainment facility, hazardous material also includes animals exposed to pathogenic organisms or biological toxins, biological specimens, animal tissues, and associated waste. A quality animal biocontainment program (BCP) results in the reduction or elimination of laboratory workers, animal care, staff and the outside environment exposure to hazardous materials. A biocontainment animal facility should have a single qualified manager who has both responsibility and authority for all animal-related activities conducted within the biocontainment envelope. The manager will need to work closely with the principal investigator, biological safety professionals, veterinarians, and facility personnel to develop the animal biocontainment program, coordinate safety training, and provide oversight

of the activities involving hazardous agents within the animal facilities.

As part of the BCP, the manager should initially develop or adopt a biosafety manual that identifies the hazards that will or may be encountered, and specifies equipment, practices and procedures designed to minimize or eliminate exposures to these hazards. When standard laboratory practices are not sufficient to control the hazards associated with a particular agent or laboratory procedure, additional measures may be needed. In those cases, safety practices and techniques must be supplemented by appropriate facility design and engineering features, safety equipment, personal protective equipment, and management practices.^{3(p1319)}

The manager plays an important role in ensuring that personnel receive appropriate training in the practices and operations specific to the animal facility and hazardous agent, such as animal handling procedures, manipulations of animals exposed to biohazards, and necessary precautions to prevent potential exposures. Working with animals in a hazardous environment increases the level of risk to personnel over standard in vitro laboratory activities through the introduction of the potential for bites and scratches and the use of sharps for injection, sample collection and necropsy procedures. The increase in risk factors requires that personnel are highly skilled in performing all the needed tasks and can operate safely in the hazardous environment. Training on task-specific activities and general biosafety are both of critical importance in order for staff to maintain a high level of safety. In addition to training, one must also include knowledge, competence and performance in order to evaluate the effectiveness of training. Knowledge is how well students understand what is being taught; competence is demonstrating how to accomplish each task successfully under controlled circumstances; and performance is what is done under actual work conditions in the laboratory or animal facility.⁴ There are many approaches to implementing an effective training program and most institutions use a combination of activities, such as didactic sessions, online modules, personal mentoring, tests, and hands-on demonstration. The training program should also include a process for providing routine refresher training and ensuring that training is documented in accordance with the many regulatory agencies and guidelines that apply to the type of work being performed.⁵ It is important that all personnel that have access to areas in which hazardous materials are used are included in the appropriate aspects of the training program.

There should be standard operating procedures (SOPs) for working with biohazards and infected animals, and each person having contact with the agent or infected animal should understand the SOPs, know the anticipated outcomes associated with the agent in use, be adequately trained in handling exposed animals, be determined competent to perform all procedures and be properly supervised. Each person providing care for the animals or carrying out experimental procedures must be alert to the hazards and understand how to perform the procedures properly and safely. SOPs and safety requirements are developed before the project has started and involves the scientist, or principal investigator, who is trained and knowledgeable in appropriate laboratory techniques, safety

procedures, and hazards associated with handling the infectious agents. This is especially true if a project is proposed that involves the use of an agent that has not been previously used in the facility or has not been studied in animals. A prestudy safety meeting with all personnel that takes all of these issues into consideration is an important part of the ability to effectively communicate risks and measures to mitigate the hazards. As the study progresses, regular safety meetings with all involved staff will help to identify and resolve new risks and issues as they arise.

There should also be procedures and processes in place to prepare for potential emergencies and disasters. The need for a disaster or emergency plan for animal facilities is universally prescribed by professional organizations, such as the American Veterinary Medical Association (AVMA), regulatory agencies, and those oversight bodies that use the *Guide* as its primary standard for evaluating animal care and use programs, such as AAALAC International and the NIH Office of Laboratory Animal Welfare.^{2(p35),6,7} The *Guide* requires that institutions develop disaster plans that take into account the well-being of animals and personnel during unexpected events and that location-based risk should be accounted for in the disaster plan. The BMBL states that biocontainment facilities should give advance consideration to emergency and disaster recovery plans, as a contingency for man-made or natural disasters. In all cases, it is prudent to conduct a thorough site-specific risk assessment based on location-specific natural disasters and common emergency situations to minimize any potential harm to animals, the environment, and/or the public when hazardous materials are involved.⁸

3 | EQUIPMENT/FACILITY CONSIDERATIONS

3.1 | Safety equipment

One of the basic principles of biosafety is the concept of primary and secondary barriers to contain pathogens to protect personnel and the environment. Primary barriers may include safety equipment and items worn for personal protection, such as gloves, gowns, shoe covers, respirators, and eye protection. Secondary barriers are incorporated into the design and construction of the facility and may include features such as autoclaves, specialized ventilation that provides directional airflow, air filtration, controlled access zones, or airlocks located at laboratory entrances.^{1(p23)}

The biological safety cabinet (BSC) is the principal device used to contain biohazards and is considered a primary barrier. Biosafety cabinets are designed to protect the individual using the cabinet and the environment through the use of directional air flow and high efficiency particulate air (HEPA) filtration. To be effective, a BSC must be well maintained, regularly tested and certified using an appropriate standard.⁹ Personnel must be trained to use them properly. According to the BMBL, those procedures that involve the manipulation of infectious materials must be conducted within biological safety cabinets, or other physical containment devices that provide the same level of protection. There are 3 classes of BSCs: I,

II, and III and a full description of these cabinets can be found in the BMBL.^{1(p291),10} A biosafety professional must be consulted to ensure that the correct type of BSC for the agent, animal species, and activities that are being performed is selected.

3.2 | Animal housing and movement

As stated above, working with hazardous agents is usually done within a BSC to contain the agent. When infected animals are considered the “hazardous agent,” a primary concern is how to contain the hazard. Procedures, such as cage changes or inoculations which may generate aerosols or expose the individual to the agent, should be performed in a BSC. Since the animals themselves are rarely housed in BSCs, they must be housed in a caging system that provides a primary barrier. Types of animal caging may include static microisolator, individually ventilated, or other biocontainment caging systems that provide a primary barrier. In situations where large animals (eg, cattle, horses, sheep) cannot be readily housed in primary containment cages the facility barriers act as the primary barriers. A clear understanding of the agent, its infectivity, and the route(s) of transmission in the species of animal being utilized is critical in determining the best way to manage the hazard.

Ventilated caging systems under negative relative pressure can be used to maintain animals that have been exposed to a hazardous agent. Usually, the air being supplied to and the air being discharged from the cage are filtered and the air being exhausted into the room is HEPA filtered or connected to the building ventilation system, thereby protecting the room environment, other animals and the workers. In either case, the rack should be designed to “fail safe” by going neutral or static to prevent exposure in the event that the power supply is disrupted. Ventilated caging systems must be designed to prevent the escape of infectious agents from the cage and the exhaust plenums during use or if the ventilation system becomes static. The system should also be alarmed to indicate operational malfunctions and alert personnel to potential hazards. Cages should only be opened or changed in a biosafety cabinet to prevent exposure to the agent or infectious waste. HEPA filters on ventilated cage systems should be tested on a regular basis to certify their effectiveness.

Biocontainment caging has been developed for both rodent and larger animal species to house animals exposed to highly infectious agents. Biocontainment caging provides a high level of protection for personnel and the environment when used properly. Some systems use cages that are completely sealed, and in the event of a power outage or motor failure may have a limited air supply. Having backup emergency power for these units, such as a generator or a battery backup system, is an important consideration. Other considerations for using some types of primary containment caging for larger animals involve isolation of the animal, animal handling, cage sanitation, experimental requirements, and veterinary-related concerns about animal well-being.

An alternative to individually ventilated, primary containment caging or housing systems is the use of flexible film



isolators or panels that surround the cage and/or rack. These units are maintained under negative pressure using exhaust motors with HEPA filters to exhaust back into the room or by exhausting to the outside through the facility HVAC. These units have been used in combination with conventional caging systems and/or when housing multiple species or agents within the same area.

Movement of infected animals within a facility should be performed with careful coordination and risk assessment. The main concern is the containment of the hazard and animal located within the transport device in order to prevent inadvertent release, including escape, of the animal or the agent. A number of transport devices have been utilized, from filtered rodent microisolator caging to transport small animals to specialized mobile HEPA filtered enclosures for multiple cages of rodents and larger animals. The primary containment transport device should be a durable, leak proof container that can be secured for transport, allows sufficient air exchange to support the physiological needs of the animal(s), and the interior and exterior of the containment device should be easily disinfected.

3.3 | Animal facility

As stated earlier, the facility provides secondary containment of the hazard and incorporates barriers into the design and construction of the facility that may include features such as autoclaves, specialized ventilation that provides directional airflow, air filtration, controlled access zones, or airlocks located at laboratory entrances.^{1(p23)} Facilities in which biohazards are used should meet or exceed the standards set forth in the BMBL. Table 1 summarizes the containment equipment and procedures recommended by the BMBL for research involving infected vertebrates. Four animal biosafety levels (ABSL-1, 2, 3, and 4) are identified, with ABSL-1 being the lowest level of containment and ABSL-4 being the highest. There are additional requirements for handling high consequence livestock pathogens, BSL-3 Agriculture (BSL-3-Ag). BSL-3-Ag, requires a different level of containment because of the necessity to protect the environment from high consequence livestock pathogens and to accommodate studies that are conducted with agricultural animals for which primary containment caging is neither practical nor available. The determination of the appropriate animal biosafety level requires experience and professional judgment and should be made in consultation with a biosafety professional and based on a thorough risk assessment of the agent and how it is going to be used. Even different projects involving the same microorganism or toxin might have a different level of risk because of the animal species involved, the route of exposure, and the activities or procedures being performed.

An important facility consideration is the heating, ventilation, and air conditioning (HVAC) system. For biocontainment facilities, the HVAC system is considered a means of secondary containment and must be able to maintain the facility under negative pressure, thereby containing the hazardous agents and preventing

any accidental release into the environment. This is usually accomplished with HVAC systems that have automated controls on the intake and exhaust valves creating directional airflow from areas that do not have pathogens to areas that do. Their use is particularly important at ABSL-3 and ABSL-4 because the agents assigned to those levels may transmit disease by the inhalation route and can cause life-threatening disease. HVAC systems require careful monitoring, periodic maintenance to sustain operational integrity, and routine verification to ensure proper directional air flow. Loss of directional airflow compromises safe laboratory operation and HVAC systems should be redundant and designed to prevent inadvertent positive pressurization from occurring during an HVAC failure.

3.4 | Personal protective equipment

While engineering controls provide a barrier between the individual and a hazard, the use of personal protective equipment (PPE) is the final physical barrier used to prevent exposures to hazardous materials and should not be used in lieu of appropriate engineering controls. Many types of PPE are available and their use should be risk-based and determined through a risk assessment process that takes into consideration specific knowledge of the potential hazards, activities being performed, engineering controls in place, experience, and sound professional judgment. Requirements for PPE should be clearly identified, consistent with the hazard and the required level of containment, and posted, so that personnel entering the room or area are aware.

PPE comes in many forms and some common items include scrubs; solid-front laboratory gowns; jumpsuits; sleeve covers; hair bonnets; safety glasses; shoe covers; examination gloves; respiratory protection; and a multitude of specialty safety items. While PPE comes in many forms and each item serves an important purpose, working with animals, sharps, and infectious agents and toxins together make gloves and respiratory protection critical considerations.¹¹ Glove material must provide an adequate barrier against the expected hazard. For example, the choice of latex or nitrile gloves may depend on the resistance to penetration if using a solvent or chemical, and the additional use of bite or cut-resistant outer gloves may be necessary if handling animals that pose a bite or scratch risk. The use of Kevlar® sleeve protectors can be useful in preventing scratches when handling larger animals, like rabbits that pose a significant scratch risk from the combination of powerful hind legs and toenails that can easily penetrate most standard PPE. People subject to a risk of an aerosol exposure to infectious agents or toxins must be provided appropriate respiratory protection. When the use of a respirator is required, the institution must implement a respiratory protection program and have a dedicated program administrator.¹² Personnel required to wear a respirator must be enrolled in a respiratory protection program that includes medical clearance to wear a respirator, fit testing, and training on its proper use and disposal, or disinfection, maintenance, and storage if reusable.

TABLE 1 Recommended animal biosafety levels (ABSLs) for activities in which experimentally or naturally infected vertebrate animals are used^a

Animal biosafety level	Agents	Practices	Primary barriers and safety equipment	Facilities (secondary barriers)
1	Not known to consistently cause disease in healthy adults	Standard animal care and management practices, including appropriate medical surveillance programs	As required for normal care of each species • PPE: laboratory coats and gloves; eye, face protection, as needed	Standard animal facility: • No recirculation of exhaust air • Directional air flow recommended • Hand-washing sink is available
2	<ul style="list-style-type: none"> • Agents associated with human disease • Hazard: percutaneous injury, ingestion, mucous membrane exposure 	ABSL-1 practices plus: <ul style="list-style-type: none"> • Limited access • Biohazard warning signs • "Sharps" precautions • Biosafety manual • Decontamination of all infectious wastes and animal cages prior to washing 	ABSL-1 equipment plus primary barriers: <ul style="list-style-type: none"> • Containment equipment appropriate for animal species • PPE: Laboratory coats, gloves, face, eye and respiratory protection, as needed 	ABSL-1 plus: <ul style="list-style-type: none"> • Autoclave available • Hand-washing sink available • Mechanical cage washer recommended • Negative airflow into animal and procedure rooms recommended
3	Indigenous or exotic agents that may cause serious or potentially lethal disease through the inhalational route of exposure	ABSL-2 practices plus: <ul style="list-style-type: none"> • Controlled access • Decontamination of clothing before laundering • Cages decontaminated before bedding is removed • Disinfectant footbath, as needed 	ABSL-2 equipment plus: <ul style="list-style-type: none"> • Containment equipment for housing animals and cage dumping activities • Class I, II, or III BSCs available for manipulative procedures (inoculation, necropsy) that might create infectious aerosols. • PPE: appropriate respiratory protection 	ABSL-2 facility plus: <ul style="list-style-type: none"> • Physical separation from access corridors • Self-closing, double-door access • Sealed penetrations • Sealed windows • Autoclave available in facility • Entry through ante-room or airlock • Negative airflow into animal and procedure rooms • Hand-washing sink near exit of animal or procedure room
4	<ul style="list-style-type: none"> • Dangerous/exotic agents which pose high risk of aerosol transmitted laboratory infections that are frequently fatal, for which there are no vaccines or treatments • Agents with a close or identical antigenic relationship to an agent requiring BSL-4 until data are available to redesignate the level • Related agents with unknown risk of transmission 	ABSL-3 practices plus: <ul style="list-style-type: none"> • Entrance through change room where personal clothing is removed and laboratory clothing is put on; shower on exiting • All wastes are decontaminated before removal from the facility 	ABSL-3 equipment plus: <ul style="list-style-type: none"> • Maximum containment equipment (ie, Class III BSC or partial containment equipment in combination with full body, air-supplied positive-pressure personnel suit) used for all procedures and activities 	ABSL-3 facility plus: <ul style="list-style-type: none"> • Separate building or isolated zone • Dedicated supply and exhaust, vacuum, and decontamination systems • Other requirements outlined in the text [CDC-NIH 2009]

^aFrom CDC-NIH 2009.

4 | PROCEDURAL CONSIDERATIONS

4.1 | Sharps

A common hazard working with animals is the need for sharps, such as syringe needles, scalpels, surgical instruments, etc. Good sharps handling practices, demonstrated proficiency, and having an awareness of the risks associated with handling sharps in a biocontainment

environment that may be contaminated with infectious material are important considerations. A standard practice is that needles should not be recapped. If procedures necessitate the repeated use of a single syringe and needle, a plastic tube (eg, 50 mL Falcon tube) or a small plastic beaker can be used to safely cover the sharp end of a needle if needed between uses.¹³ In the containment area, additional practices include using a pair of forceps to remove needle caps; always directing the needle away from the individual; having an

appropriately sized sharps container positioned within arm's reach, and in a manner that prevents crossing over of arms or hands to dispose of sharps; and if more than 1 person is working with sharps nearby or within the same biosafety cabinet, each person should have their own sharps container. Sharps containers should be discarded when they are two-thirds to three-quarters full. Performing necropsies on infected animals requires special consideration for hand protection, such as cut-resistant outer gloves, due to the high risk that comes from frequent use of scalpels and other sharp instruments. Newer technologies, including retractable scalpels that cover the scalpel blade when not in use and integral needle safety technologies, such as self-retracting needles and no-touch sheath covering devices, can reduce the risk of injury if used as designed.

4.2 | Waste disposal

Waste streams must be clearly identified to ensure the proper decontamination and disposal of all types of waste generated in animal rooms and support areas within a containment facility. The types of waste streams can vary based on the activities being performed; therefore, each institution should identify and define their waste streams and implement appropriate decontamination and disposal procedures for each stream. Knowledge of the multiple national, state and local regulations that apply to the identification of waste streams, decontamination, handling, transportation and disposal of biohazard waste is critical to ensure compliance. The use of commercial hazardous waste disposal companies to help with navigating the myriad of regulatory requirements for waste disposal has become a common practice. These companies can be an excellent resource for obtaining training on identifying waste streams and for help with developing internal waste handling procedures that meet regulatory requirements.

4.3 | Sanitation procedures

In animal husbandry, sanitation is the maintenance of environmental conditions conducive to the health and well-being of the animal, and involves bedding changes, cleaning, and disinfection.^{2(p69)} Environmental conditions include both the primary caging and secondary room environments in which animals are maintained. Maintenance of those conditions involves activities such as changing cages and bedding, as well as routine sanitation of animal caging, racks, and the secondary environment. Cleaning and disinfection are important aspects of any sanitation program and the difference between the 2 methods should be understood in a biocontainment environment.^{3(p1305)} Cleaning is the removal of excessive amounts of gross contamination caused by animal waste, dirt, and debris, while disinfection is the reduction or elimination of unacceptable concentrations of microorganisms.^{2(p69)} Neither method is designed to sterilize the environment. These activities in biocontainment may be slightly different than in a conventional area. For example in most biocontainment facilities, the cage wash is located outside of the biocontainment area, so caging and waste must be sterilized prior to removal from the containment area.

Cleaning in biocontainment may be complicated by the need to clean in place due to facility and/or protocol constraints, the use of complex biocontainment caging, and the requirement to minimize aerosol formation. Some caging, such as biocontainment caging for larger, nonrodent species, may have to be partially disassembled to allow for adequate cleaning. Cleaning in biocontainment is usually performed by hand without the use of a mechanical washer. Caging should be adequately rinsed after cleaning to prevent exposure of the animals to residual chemicals. When using hand-washing to clean cages in lieu of a mechanical washer, evaluating the effectiveness of the sanitation procedures is recommended.^{2(p72)}

Disinfection of primary and secondary enclosures in containment usually involves the use of chemical disinfectants during the conduct of the study and chemical, gas or vapor disinfectants between studies. The type of chemical disinfectant used must be carefully considered as it must be effective against both naturally occurring microorganisms in the environment and those that are used experimentally. Appendix B of the BMBL provides guidance on classes of disinfectants and selection of the type of disinfectant to use.^{1(p326)} Ultimately, a biosafety professional should be involved in the selection of an appropriate disinfectant for use in the facility, based on a risk assessment. Validation studies may be required to verify the effectiveness of the disinfectant against the microorganism and the appropriate contact time.

4.4 | Animal handling and restraint

Animals exposed to infectious diseases present a concern to individuals handling the animal due to the risk of transmission of the agent from the animal to the handler. Transmission could occur by a variety of methods, to include bites, scratches, needle sticks, mucous membrane exposure, or aerosol transmission. The use of physical restraint devices (squeeze cages or restraint boxes), chemical restraint, additional PPE as previously described, and practices that reduce the risk of exposure during animal manipulations should be used whenever possible. According to the BMBL, all procedures involving the manipulation of infectious materials (either the infectious agent or tissues from infected animals), handling of infected animals or the generation of aerosols must be conducted within BSCs or other physical containment devices when practical. BSCs are commonly used with small rodents, but present a challenge when handling larger laboratory animal species and are impractical for agricultural animals. When a procedure cannot be performed within a biosafety cabinet, a combination of personal protective equipment and other containment devices or methods must be used. Depending on the species of animal and/or procedure being performed, more than 1 person may be required to work safely.

5 | GUIDELINE CONSIDERATIONS

5.1 | Oversight of animal research involving biohazards

Research involving hazardous agents, including pathogenic organisms, toxins, and biological materials from infected animals, requires

careful consideration during the review process. To ensure compliance with all applicable laws and regulations, research involving hazardous agents may be reviewed and approval granted by a number of different groups prior to the conduct of the study. The review includes the Institutional Animal Care and Use Committee (IACUC) if animals are involved and the Institutional Biosafety Committee (IBC) if biohazardous agents are involved. Additional regulatory approval may be required based on national or state requirements for the work being conducted.

5.2 | Institutional animal care and use committee

The ultimate responsibility for review and approval of animal use protocols lies with the IACUC^{2(p25),14,15} or similar ethical review committee. It is important that there are members of the IACUC that have the background and experience to adequately review protocols involving biohazards or the committee should have access to a biosafety professional who is knowledgeable about the biohazards that will be used. Many institutions have someone from the institutional biosafety program to serve as a member of the IACUC. Alternatively, an appropriate biosafety professional could serve as an ad hoc reviewer for the committee. During the review process, it is important to have adequate information about the biohazard and protective measures. Many institutions have adopted the use of a biohazard appendix to the protocol form to assist in the review process. The biohazard appendix is tailored to the needs of the institution.

5.3 | Institutional biosafety committee

Institutions have safety offices and committees that review the use of hazardous agents, including chemicals, biological agents, and radioactive materials. Institutions that receive federal funding from the NIH to work with recombinant or synthetic nucleic acid molecules are also required to comply with the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*. A requirement of these guidelines is the establishment of an institutional biosafety committee (IBC) that includes individuals with experience and expertise in recombinant or synthetic nucleic acid technology, biosafety and physical containment. The committee must also have a biological safety officer if work is being conducted at ABSL3 or ABSL4 and a member with expertise in animal containment if experiments with animals are being performed. The *NIH Guidelines* provide guidance on physical and biological containment practices for recombinant or synthetic nucleic acid molecule research involving etiological agents and animals. Experiments with recombinant or synthetic nucleic acid molecules and animals could include the creation of transgenic animals as well as the use of manipulated biological agents in animals. Either situation makes the risk assessment and review more difficult because the disease process and pathogenesis in the animal may be altered, thereby requiring additional containment measures.

6 | OCCUPATIONAL HEALTH CONSIDERATIONS

6.1 | Occupational health and safety program

Institutions have a responsibility for ensuring worker safety. An essential part of an institution's safety program is an occupational health and safety program (OHSP) that is consistent with national, state, and local regulations and focuses on maintaining a safe and healthy workplace. An effective OHSP takes into consideration all facets of the research program including facilities, personnel, research activities, biohazards, and animal species, and includes careful coordination with members of the research, animal care and use, occupational health, safety, and administration groups. There are a number of references to utilize when establishing an OHSP for personnel working with hazardous agents and include the *Guide for the Care and Use of Laboratory Animals* and the National Research Council's Publication *Occupational Health and Safety in the Care and Use of Research Animals*. For those facilities working with infectious agents and biological toxins, guidance is provided in the BMBL^{1(p114)} and the *NIH Guidelines*.¹⁶ Components of an occupational health program include preplacement medical evaluations, vaccines, periodic medical evaluations, and medical support for occupational illnesses and injuries.^{1(p115)}

6.2 | Preplacement medical evaluations

Workers who may be exposed to biohazardous agents and toxins should be enrolled in an OHSP and receive a preplacement/preassignment medical evaluation.^{1(p115),13,17(p7)} Determining which personnel will be provided occupational healthcare services is not based solely on job titles and classifications, but rather is based on a risk assessment of potential exposure.¹⁸ Healthcare providers should be cognizant of potential hazards encountered by the worker, and have an understanding of the potential health hazards present in the work environment. Optimally, there should be ready access to an infectious disease physician with understanding of the hazards presented by the agents used within the facility. As part of the medical evaluation, the healthcare provider should review any previous and ongoing medical problems, current medications, allergies, and prior immunizations in order to determine an individual's medical fitness to perform the duties of a specific position and what medical services are needed to permit the individual to safely assume the duties of the position. Criteria for fitness for duty should be established based upon the occupational health hazards identified from a site-specific, comprehensive risk assessment.^{19(p7)}

6.3 | Vaccines

Commercial vaccines should be made available to workers to provide protection against infectious agents to which they may be occupationally exposed. Animal care personnel are routinely vaccinated against tetanus and pre-exposure immunization is offered to people



at risk of infection or exposure to specific agents such as rabies virus (eg, if working with susceptible species) or hepatitis B virus (eg, if working with human blood or human tissues, cell lines, or stocks).^{2(p22),20} As part of the risk assessment, it should be determined if there are vaccines available for the agents present in the workplace and, if warranted, vaccination should be provided for those biohazardous agents for which effective vaccines are available. The Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) provide general vaccination and vaccine-specific recommendations.^{21,22}

6.4 | Periodic medical evaluations

Routine, periodic medical evaluations may be a part of an OHSP for personnel working with hazardous agents, and medical clearances may be required for specific circumstances (eg, respirator usage). The frequency and methods of medical evaluation may vary and are based on the needs of the program. Routine medical evaluations may be done through the use of questionnaires or through physical evaluations, depending on the level of risk present in the workplace and the health of the individual. In the interim between evaluations, it is important that individuals working in facilities with hazardous agents self-report changes in their health status that may impact their ability to work safely with the agents. It is also important to note that in special circumstances, it may be appropriate to offer periodic laboratory testing to workers with substantial risk of exposure to infectious agents to detect preclinical or subclinical evidence for an occupationally acquired infection.^{1(p119)}

6.5 | Medical support for occupational illnesses and injuries

As part of the OHSP, plans for addressing potential exposures to hazardous agents should be in place. Proper and timely postexposure response is supported by having agent and exposure-specific protocols readily available that define the appropriate first aid, potential postexposure prophylaxis options, recommended diagnostic tests, and sources of expert medical evaluation.^{19(p7)} Potential exposures can present days later with signs that are similar to common respiratory diseases. Workers should be encouraged to seek medical evaluation for symptoms that can be associated with infectious agents in their work area. Proactive reporting of clinical signs is important because infections are more difficult to treat and have greater morbidity and mortality if treatment is delayed. Fatal occupational infections have resulted from apparently unknown exposures.²³

7 | SUMMARY

The ability to work safely with animal models exposed to biohazards depends on multiple factors, several of which are presented in this article for consideration. Working in or managing an animal biocontainment program requires a thorough understanding of the basic

principles of containment, including both the engineering and procedural controls necessary to protect both personnel and the animals with which they work. Work conducted with biohazardous agents requires a thorough risk assessment, specialized equipment and procedures, and knowledgeable and well-trained personnel. Personnel must be fully aware of the highly regulated environment that accompanies this type of work and they must have a profound appreciation for the serious consequences of noncompliance. Working with animals exposed to biohazardous agents requires a high level of skill and awareness to overcome some of the challenges of the biocontainment environment, but the positive impact on society and one's own professional fulfillment can be great. While this article is not a comprehensive review of all the aspects of working with animals exposed to biohazards, it provides a basis for understanding the complexity of the environment and provides additional reference materials for anyone working in this area or considering it as a career path.

CONFLICT OF INTEREST

None.

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