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Research Article

Biosafety and data quality considerations for animal experiments with highly infectious agents at ABSL-3 facilities

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A B S T R A C T

Animal models are crucial for the study of severe infectious diseases, which is essential for determining their pathogenesis and the development of vaccines and drugs. Animal experiments involving risk grade 3 agents such as SARS CoV, HIV, M.tb, H7N9, and Brucella must be conducted in an Animal Biosafety Level 3 (ABSL-3) facility. Because of the in vivo work, the biosafety risk in ABSL-3 facilities is higher than that in BSL-3 facilities. Undoubtedly, management practices must be strengthened to ensure biosafety in the ABSL-3 facility. Meanwhile, we cannot ignore the reliable scientific results obtained from animal experiments conducted in ABSL-3 laboratories. It is of great practical significance to study the overall biosafety concepts that can increase the scientific data quality. Based on the management of animal experiments in the ABSL-3 Laboratory of Wuhan University, combined with relevant international and domestic literature, we indicate the main safety issues and factors affecting animal experiment results at ABSL-3 facilities. Based on these issues, management practices regarding animal experiments in ABSL-3 facilities are proposed, which take into account both biosafety and scientifically sound data.

1. Introduction

Animal models are crucial for the study of severe infectious diseases, which is essential for determining disease pathogenesis and the development of vaccines and drugs. Risk group 3 pathogens such as severe acute respiratory syndrome coronavirus (SARS CoV), human immunodeficiency virus (HIV), Mycobacterium tuberculosis (M.tb), H7N9 influenza virus, and Brucella cause serious or lethal human disease and present a significant public health hazard. Animal experiments involving these highly infectious agents are required to be conducted in an ABSL-3 facility.1–4 As biosafety facilities for in vivo work, ABSL-3 facilities require more complex biosafety management practices than BSL-3 facilities.5 There is no doubt that ensuring biosafety is the highest priority of animal experiment management at ABSL-3 facilities. At the same time, we cannot ignore the scientifically valuable results of animal experiments obtained in ABSL-3 laboratories. Therefore, a study of the animal experiment management practice points that takes into account data quality from a biosafety premise is of great significance. What kinds of safety management concepts should ABSL-3 laboratories take into consideration for animal experiments? What are the main safety issues and factors affecting the quality of scientifically sound data? What are the main points of management practice? We provide a preliminary discussion of the above issues based on the management experience at Wuhan University ABSL-3 Laboratory and relevant international and domestic literature.

2. Overall biosafety concept

The goal of animal experiment management at ABSL-3 is to guarantee reliable animal experimental data (scientifically sound data) while also ensuring safety. This goal has two meanings: one is “biosafety first”, which is to ensure the safety of the workers, environment, and animals in the experiments as the top consideration. The other is “quality of scientifically sound data”, which guarantees the integrity and reliability of scientific research data and ensures achieving scientific research objectives based on safety. The two elements of “biosafety” and “quality of scientifically sound data” should both be considered. Therefore, we need to establish an overall biosafety concept that ensures the safety of the animal experiments first, and then the animal care and research procedures should be optimized in order to obtain reliable scientifically sound data from the animal experiments. The overall biosafety concept needs to follow the following principles:
2.1. Combination of biosafety and animal welfare

Animal welfare is closely related to scientific quality, and good animal welfare conditions are beneficial to the reliability of scientific data. Laboratory animal welfare requires the animal to maintain physical and psychological well-being by providing living conditions in accordance with its nature, and alleviating animal stress and pain in experiments as much as possible while also achieving the study objective. Alleviating animal stress and pain can reduce aggression, the benefits being reduced aerosol contamination as well as animal scratches and bites, making workers safer. When their physical and psychological well-being is maintained, the animals minimize their stress response to the environment and manipulations. Therefore, they have more stable physiological and biochemical indicators and the results of animal experiments are more reliable.

2.2. Combination of biosafety and experimental operation

The non-human primate (NHP) is one of the most useful laboratory animals in human pathogen infectious experiments at ABSL-3. However, unlike the common commercial animal biocontainment IVC (individually ventilated isolation cage) for mice, NHP animal cages sometimes need to be customized according to the experimental demands. The customized NHP cages should be designed to meet the requirements of animal welfare and the convenience of operation while considering the biosafety. The animal biocontainment cages that make it difficult to care for animals are not applicable. Personal protective equipment (PPE) is a primary barrier used to protect workers. The PPE worn within the ABSL-3 facility may limit the worker's vision and reduce tactile sensation. These limits reduce the worker's accuracy. As a result, when the workers use needles and other sharp instruments for procedures, they have an increased chance of injury. Therefore, the Standard Operation Procedures (SOPs) and training programs should be optimized to improve the accuracy and stability of the operations according to the specific PPE requirements, and those efforts can ensure both “biosafety” and “scientifically sound data quality”.

The following are the main safety issues and factors affecting the results of animal experiments at ABSL-3. Based on these factors, we propose management practice points.

3. Major safety issues within the ABSL-3 facility

3.1. Safety issues regarding laboratory animals

3.1.1. Infected animal escape

The infectious animals may escape and cause a potential hazard to humans and the environment when cage lids or doors are not properly locked.

3.1.2. Zoonosis

The World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) define zoonotic disease as: “Epidemiology-related diseases caused by common pathogens in humans and vertebrates.” The zoonotic pathogens carried in animals are potential hazards to workers. For example, herpes B virus is usually carried in macaques, and the infected animals are asymptomatic. However, herpes B virus can be fatal to humans.

3.1.3. Animal scratches, bites, and kicks

Some invasive procedures can easily cause an excessive reaction from animals if they are not well-sedated using an analgesic or anesthetic. The workers can be scratched and bitten by the infected animals. In experiments involving large animals such as cattle and horses, the animal room is the primary barrier for biocontainment. When entering the room, the workers may invade the animal’s safe “flight distance” and cause the animal to feel trapped with no route to escape, especially within the confined space of ABSL-3 containment. Under this circumstance, the animal may exhibit aggressive behaviors, such as biting, scratching, and kicking toward the personnel.

3.2. Safety issues regarding pathogenic microorganisms

3.2.1. Infectious aerosols

In the handling of animals, changing cages, dumping bedding, etc., it is easy to produce infectious aerosols from infected animal skins, furs, and bedding. These infectious aerosols are a potential hazard to workers and the environment.

3.2.2. Sharp instruments injury

Sharp instruments such as needles, knives, and scissors are often used in animal procedures, including but not limited to animal challenge, blood collection, sampling, in vivo detection, biopsy, anaesthesia, euthanasia, and necropsy. The workers might be injured by the contaminated sharps and exposed to pathogens.

3.2.3. Infectious materials from in vivo experiments and necropsy

During in vivo experiments and necropsy, workers may be exposed to animal infectious materials such as blood, urine, feces, nasopharyngeal swabs, samples containing bacteria or viruses, body fluids, and organs of infected animals. These infectious materials are potential hazards to workers and the environment.

3.2.4. Waste and carcasses of infected animals

Waste such as animal bedding, medium containing pathogens, and carcasses of infected animals have a high risk of exposing personnel and the environment to pathogenic microorganisms.

3.2.5. Accidents

3.2.5.1. Infectious material spills and splashes. Infectious materials will cause biosafety hazards to the personnel and environment when the laboratory workers spill or splash them on the bench or ground by accident.

3.2.5.2. Infectious samples transport. Some of the samples collected from the infected animals may be assessed within ABSL-3, and others need to be transferred out of ABSL-3 for detection. Failure to safely transfer samples out of ABSL-3 poses a potential hazard to both personnel and the environment.

3.2.5.3. Transporting animals between rooms within ABSL-3. Infected animals sometimes need to be transferred from the animal room to the specific procedure room or necropsy room within ABSL-3 for related in vivo examination or necropsy. During the animal transport, the personnel and environment may be exposed to pathogens.

3.3. Physical safety issues

In some experiments, special equipment may be set up inside the ABSL-3 facility, such as X-ray, PET/CT, or NMR devices. This equipment can produce ionizing or radioactive radiation and we cannot ignore the associated physical safety issues.

3.3.1. Ionizing radiation damage

X-ray, CT, and other imaging equipment are used for providing in vivo imaging data during animal experiments. For example, both
a chest X-ray and CT scan can provide images of the lesions on the lungs in the monkey model used for studying SARS-CoV. Workers who are exposed to the X-rays from the imaging equipment may be at risk for skin, hematopoesis, and intestinal injury.\textsuperscript{12}

3.3.2. Radioactive hazards
As a method of biological and molecular imaging,\textsuperscript{9} PET/CT scanning can be used to noninvasively, quantitatively, and dynamically monitor the labeled compounds in vivo, the functional information regarding the specific organs or lesion tissues, and biological and biochemical changes in the animals. Because of these advantages, PET/CT imaging is becoming more useful in infectious animal research. However, the animals need to be injected with a radiolabeled tracer for the PET/CT scan. Therefore, the animal bedding, excrement, and carcass may contain radioactive materials. These materials present a risk to the personnel and environment.

3.4. Anesthetic issues
Anesthetics are often used in animal experiments. Anesthetics are also harmful to human health. Long-term exposure to anesthetics may cause damage to the liver, kidney, nervous system, and reproductive system.\textsuperscript{9} As an inhalation anesthetic, isoflurane has been widely used in animal experiments because of its excellent anesthetic quality. However, it may cause health problems if workers are exposed to waste anesthetic gas.

3.5. Safety issues from inadequate facilities and equipment
The primary barrier consists of laboratory safety equipment such as biosafety cabinets (BSCs), animal isolators, and personal protective equipment (PPE). The workers are protected or isolated by the primary barrier from the pathogen, infectious materials, and infected animals.\textsuperscript{13} The ABSL-3 facilities mainly include the ideal enclosure structure; floor layout (functional partition); heat, ventilation, and air conditioning system (HVAC); power supply system; automatic control/monitoring/communication system; water supply and drainage system; air supply system; and disinfection/sterilization/waste disposal system. These facilities constitute the secondary barrier that can ensure directional airflow and a negative pressure gradient promoting the air circulation from a clean area to contaminated area to prevent pathogens leaking into the outside environment. The primary and secondary barriers together achieve the two major functions of the ABSL-3 facility: protecting both workers and the environment from exposure to highly infectious pathogens. Although, in general, the facilities and equipment meet the necessary qualifications, there are biohazard risks to workers and the environment when these requirements are not met.

4. Factors affecting animal experiment results
The scientific quality is shown by the data from the animal experiments. There are three major factors that can affect the results of animal experiments.

4.1. Animal itself
There are different features regarding anatomy and pathophysiology in different animal species. Different species respond differently to test materials. The sex, age, weight, and physiologic health condition of the animals can also affect the experiment results. Healthy laboratory animals have better tolerance to various stimuli than unhealthy animals.

4.2. Animal housing environment and nutritional factors
The animal housing environmental factors including temperature, humidity, air change rate, air cleanliness, light, and noise have effects on the health of experimental animals.\textsuperscript{14,15} Adequate nutrition is the foundation for growth, development, and enhancing disease resistance. The results will be unreliable if the animals involved in the experiment are malnourished.

4.3. Worker proficiency and technical procedures involving laboratory animals
Workers engaged in animal experiments need to have specialized expertise and skills, including methods for establishing animal models, selection of laboratory animals, grouping of experimental animals, and techniques for specific experimental animal species, which include but are not limited to animal capture, restraint, blood collection, sampling, anesthesia, surgery, necropsy, and pathological biopsy. The method of establishing an animal model and the animal species will define whether you can achieve the objective of the study. The number of animals is related to the statistical analysis and the reliability of the data. The rationality of animal grouping and a controlled setting make the study results more convincing. Using the proper agents, method, and concentration of compounds for anesthesia is important to ensure that the experiment will be completed successfully and reliable results will be obtained. Proper surgical methods and skilled techniques are also important for obtaining credible experimental data. Moreover, experiments have shown that body temperature, blood pressure, heart rate, blood glucose, basal metabolic rate, hormone secretion, central nerve transmitters, and bioactive substances from blood, urine, and saliva of the laboratory animals all exhibit circadian rhythm changes.\textsuperscript{9} Therefore, all the animals should be treated at the same time points to make sure that the results are comparable.

5. Key elements of animal experiment management practices at ABSL-3
Under the guidance of the overall concept of safety, focusing on the two goals of “biosafety” and “scientifically sound data quality” for ABSL-3 management, we indicated above the safety issues and factors affecting scientific results at ABSL-3. According to our experience and relevant international and domestic literature, we propose the following key elements of management practice at ABSL-3, which reflect both the safety (workers and environment) and ability to obtain scientifically sound data.

5.1. Review of animal use protocol
The Institutional Biosafety Committee (IBC) and the Institutional Animal Care and Use Committee (IACUC) are organizations that ensure the “biosafety” and “scientifically sound data quality” of ABSL-3 animal experimental activities. Before the start of the experiment, the Principal Investigator (PI) of the study must fill in the Animal Use Protocol (AUP) and submit it to the IACUC and IBC for review. The project is not allowed to start unless the AUP is approved by the IACUC and IBC. The key review points of the IACUC are the same as in normal animal experiments. The key review points of the IBC are as followed:

5.1.1. Training and experiences of project team members
The contents of training include biosafety, knowledge of laboratory animals, husbandry, technical procedures regarding laboratory animals (especially for specific animal species involved the
study), and animal welfare. All of the above training must be complete before starting the study.

5.1.2. Health and safety of workers

Review what the safety hazards (biological, physical, chemical) involved in this animal experiment are and how to prevent hazards to workers.

5.1.3. Disposal of animal carcasses and waste

All the waste and carcasses must be decontaminated (e.g., autoclaved) and then they can be taken out of the ABSL-3-containment areas.

5.2. Laboratory management practices

Selection of healthy and qualified laboratory animals for the experiment, correct management and feeding of animals, good nutrition, and maintaining health will help guarantee the biosafety and allow for the obtaining of accurate data in the experiment.

5.2.1. Procurement of healthy laboratory animals from the qualified laboratory animal suppliers

The laboratory animals should be procured from the laboratory animal suppliers who have a production license for laboratory animals. The qualified suppliers will provide the quality certificate of animal suppliers who have a production license for laboratory animal suppliers.

5.2.2. Set the quarantine and acclimation periods for the laboratory animals

There should be a quarantine period for the laboratory animal when they arrive at the facility. During the quarantine period, the veterinarian will do clinical observations and screening to ensure that the animals are in good health and are suitable for the experiment. The animals without abnormalities during the quarantine period can be used in the experiment. When the animals are transferred to the animal room within ABSL-3, they need to go through an acclimation period so that the animals can acclimate to the new housing facility surroundings such as new cages and negative pressure in the biocontainment areas. This will stabilize both the physical and psychological status of the animal. This stability makes the experimental results more reliable.

5.2.3. Scientific laboratory animal care

Animal care procedures mainly include feeding the animal, providing the animal with drinking water, changing bedding/cages/water bottles, cleaning/disinfecting the breeding room and cages, disposal of the animal waste, and recording the status of the animal health and activities. The animals should be in the animal isolators such as the IVC, if possible. If the cages or the fences need to be customized, the products should be easily operated or maintained, easily cleaned and disinfected, have low failure rate, impact and bite resistance, be free of sharps and burrs, and easily observable while still meeting the biosafety criteria. This can provide a clean, comfortable, and safe environment for the animals. The animal should be fed with clean and high-nutrition feed and sterilized drinking water based on the animal's behavior and the requirement of the experiment. The water bottles, bedding, and cages should be cleaned and disinfected at appropriate intervals. The animals in the blank control group should be handled first and those in the infection group later in order to avoid cross-contamination. While handling mid-size or large animals, workers need to interpret how an animal will respond by observing posture, behavior, or other subtle signs. Interpretation ability is critical to maintain personnel safety and prevent workers from animal injury.

5.2.4. Prevent infected animals from escaping

The door or cover of the cage should generally have a precaution device to prevent animals (such as monkeys) from accidentally escaping by opening the cage themselves. During animal care and manipulation, the workers should be proficient in various methods of handling the animal. Workers should cover the cage, lock the cage door, and prevent infected animals from escaping.

5.2.5. Set the device to prevent wild mice and pests from entering

There should be a limitation device at the entrance of the animal facility to prevent wild mice and pests from entering.

5.3. Safety management practices

5.3.1. Safety management involving pathogenic microorganisms

5.3.1.1. Personnel access management. Access to ABSL-3 facilities is restricted. Only authorized personnel can enter ABSL-3 designated areas. The people who enter the ABSL-3 facility must master and adhere to standard operating procedures (SOPs) for entry, exiting, and donning and taking off PPE. PPE worn by personnel in large animal handling areas must allow for freedom of movement in order to prevent the PPE from being broken during strenuous activities such as restraint and handling of animals.

5.3.1.2. Protection against infectious aerosol. When dealing with infected animals and infectious materials, the workers should act carefully in order to reduce the production of aerosols. Animals should be housed in isolation cages as much as possible, such as mouse IVCs. In any case, IVC change and experimental procedures should be performed within the BSC, if possible. Otherwise, a combination of the appropriate PPE (e.g., positive air purifying respirator, PAPR) and other containment devices should be used based on the risk assessment.

5.3.1.3. Safe use of sharps. Sharps are often used in animal experimental procedures such as blood collection, and necropsy. The researchers and technicians should be proficient in the procedures for the safe use of sharps. Use a syringe with a protective cap within the ABSL-3 facility. After use, the needle must not be recapped. Used disposable needles must be carefully placed in puncture-resistant containers for disposal. It is not recommended to use pins to restrain mice at ABSL-3. The instruments for necropsy such as forceps and scissors should have a blunt end whenever possible. The scalpel should have a protective cap. Try to avoid the use of glass products. If glass is broken, workers should use tweezers to pick up the pieces and not their hands.

5.3.1.4. Avoid being bitten or scratched by animals. During the animal experiment, the animals should be physically (restrain device) or chemically (anesthetic) restrained, and the workers should use proper PPE to avoid being bitten or scratched by animals. Two workers should enter the animal room and work together to prevent animal attacks. For social animals such as monkeys, in addition to providing non-social enrichments such as a puzzler device, perch, and monkey mirrors, it is also important for animals to be provided social enrichment, meaning that animal workers should not be replaced frequently in order to avoid animal stress in response to strangers. In addition, the workers may have positive interactions with the animals, if possible. These social enrichments may reduce the animal's stress response and aggression. Under these circumstances, the workers are safer, and the results are...
more stable and reliable. If necessary, positive reward training can be used to train animals to adapt to cages and experimental procedures. This training may provide assurance for worker safety and conducting the experiment more smoothly.

5.3.1.5. Develop good SOPs for animal experiments involving highly infectious agents. Staff should be proficient in the experimental procedures for infected animals, including, but not limited to: BSC operation, preparing the pathogen stock for challenge, animal holding, operation of restraint device, anesthesia, animal challenge, in vivo detection, blood collection, sampling, surgery, euthanasia, necropsy, biopsy, transport of infectious materials, transfer of infected animals, daily cleaning and disinfection for animal and procedure rooms, terminal disinfection for the facility, disposal of animal carcasses and waste, and response to emergency accidents. Excellent technical ability of workers guarantees the safety and reliability of experimental results.

5.3.1.6. Safe disposal of waste. All the solid and liquid waste produced from animal experiments must be decontaminated (e.g., autoclaved) before removal from the ABSL-3 containment areas.

5.3.1.7. Response to emergency accidents. It is necessary to develop an emergency response protocol for all accident scenarios that may occur in animal experiments. Training and practice drills for the protocol should be carried out regularly.

5.3.2. Safety management practices for chemicals

The laboratory should make material safety sheets (MSDS) for chemical disinfectants that are used in the ABSL-3 facility. MSDS should include the detailed information about the potential hazards, emergency medical procedures, and first-aid equipment. The containers for chemical compounds should be marked with the generic names and ingredients. Anesthetics need be managed by specific personnel and used by registration. Because the enclosure structure of ABSL-3 has high air tightness, the scavenger for waste anesthetic gas should be set when a volatile anesthetic such as isoflurane is used in an ABSL-3 facility in order to protect the workers from the waste gas. In addition, we can connect the anesthesia machine and the BSC with an annular tube and perform the anesthesia within the BSC.

5.3.3. Safety management practices for physical hazards

Workers should utilize personal protection to avoid exposure to UV. The X-ray and CT machines should be set up inside a room with a safety protection barrier. The operators should wear appropriate protective equipment. The bedding and other waste containing radioactive materials should first be put in a safe place within the ABSL-3. This waste cannot be autoclaved and taken out of the ABSL-3 facility until the radioactivity in the waste drops to permissible levels. The animal carcasses that contain radioactive materials should first be packed in a special plastic bag for radioactive materials. Then, the carcasses will be dried at 60–70°C for several days. The dried carcasses can then be treated following the protocol for dealing with radioactive waste.

5.3.4. Facility and equipment management

For the facility and equipment, the emphasis is on “maintenance” rather than “construction” of the ABSL-3 facility. In China, in the majority of ABSL-3 facilities, most of the staff have a biomedical background. There is a shortage of personnel for facility and equipment maintenance in ABSL-3 facilities. The key factor to keep the ABSL-3 facility running smoothly is to establish a professional team for the facility and equipment maintenance personnel based on the actual institute situation and the national situation of China.

5.3.5. Personnel training

The excellent professional competence of ABSL-3 laboratory personnel is the fundamental guarantee for “biosafety” and “scientifically sound data quality”. Excellent skills are achieved through scientific and effective training and repeated practice. ABSL-3 animal experiment training courses generally include theoretical and practical (hands-on) training. Hands-on training is essential. It is the most important, and should make up at least 2/3 of the total training time. Only those who are competent in both theoretical and experimental operations training can participate in animal experiments. The staff in the ABSL-3 laboratory should have the following knowledge and/or skills: relevant national regulations, ABSL-3 laboratory policies, professional knowledge and procedures for laboratory animals, biosafety, and animal welfare. The training for ABSL-3 is “specific” and “multistep”. “Specific” refers to the training that is for the specific experiment, animal species, and experimental procedures. For example, workers who are qualified for regular mouse experimental operating procedures training are not necessarily also qualified for experimental operation of other animal species such as rabbits and monkeys. He/she also might not be qualified for some special mouse experimental operations. The worker should have access to the technology needed for the animal species and procedures approved by the IACUC and IBC. Otherwise, he/she is not allowed to participate in this experiment. “Multistep” training courses are created for midsize and large animals. Such animal experiment training starts from the low level and increases to the high level according to the difficulty degree of the SOPs. Trainees who have mastered the lower level technology may be allowed to join the higher-level training course. After the training, the trainee must pass a strict examination authorized by the experienced trainer before obtaining a competency certificate. The worker who obtains the certificate should work with an experienced worker first until he/she can operate safely. All the animal experiments need to be conducted by at least two workers.

6. Conclusion

The management goal of the ABSL-3 laboratory is to ensure the safety of animal experiments with highly infectious agents and to obtain high-quality experimental data. In order to achieve this goal, we need to establish an overall concept of biosafety, which has both comprehensive considerations for safety (worker, environment) and data quality. Those two aspects are critical for successful implementation of animal experiments at ABSL-3. We need to take comprehensive measures to address the AUP review, laboratory animal management, laboratory safety management, facility and equipment management, and personnel training. All these measures can guarantee both the safety of ABSL-3 and credible scientific animal experiment results.

Conflict of interest statement

The authors declared that they have no conflicts of interest to this work.

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Appendix A. Supplementary data

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References

1. World Health Organization. Laboratory Biosafety Manual. Geneva, 2004.
2. Order No. 424 of the State Council of the People’s Republic of China. Regulations on Biosafety Management of Pathogenic Microorganisms Laboratory. Beijing, 2004.
3. Ministry of Health of the People’s Republic of China. List of Pathogenic Microorganisms Transmitted by Humans. Beijing, 2006.
4. U.S. Public Health Service Centers for Disease Control and Prevention and National Institutes of Health. Biosafety in Microbiological and Biomedical Laboratories (5th ed.). Washington: U.S. Government Printing Office; 2007.
5. General Administration of Quality Supervision, Inspection and Quarantine of the People’s Republic of China, National Standardization Administration Committee. National Standard of the People’s Republic of China General Requirements for Laboratory Biosafety (GB19489-2008). Beijing: China Standard Press; 2009.
6. He Zhenming, Xing Ruichang, Fang Xiye, et al. The laboratory animal welfare, animal experiments and the replacement of animals. Lab Anim Sci Manage. 2005;22:61–64.
7. Powell Diana S, Walker Reagan C, Heflin Dennis T, et al. Development of novel mechanisms for housing, handling, and remote monitoring of common marmosets at animal biosafety level 3. Pathog Dis. 2014;71:219–226.
8. Qin Chuan. Laboratory Biosafety Accident Prevention and Management. Beijing: Science Press; 2017.
9. Qin Chuan. Laboratory Animal Sciences. Beijing: People’s Medical Publishing House; 2010.
10. Bayne Kathryn. Enrichment for Nonhuman Primates. Office of Laboratory Animal Welfare at NIH, U.S. Department of Health and Human Services; 2005.
11. Olsen SC. Biosafety considerations for in vivo work with risk group 3 pathogens in large animals and wildlife in North America. Anim Health Res Rev. 2013;14:2–10.
12. Lu Bing, Lv Jing, Zheng Tao. Basic Knowledge of Laboratory Biosafety. Beijing: China Metrology Publishing House; 2004.
13. Zhao Suqing, Wang Hua, Li Ping. Laboratory Facilities and Equipment for Biosafety. Beijing: Military Medical Press; 2017.
14. Wang Luzeng, Li Hua, Wang Jie, et al. Influence and control of ventilation, temperature and humidity on laboratory animal welfare. Chin J Comp Med. 2004;14:234–236.
15. Shi Xiaoping, Li Hua, Wang Jie, et al. Effects of noise, illumination and air quality on the welfare of laboratory animals. Lab Anim Sci Manage. 2006;23:63–64.
16. General Administration of Quality Supervision, Inspection and Quarantine of the People’s Republic of China, National Standardization Administration Committee. National Standard of the People’s Republic of China, Laboratory Animal Environment and Housing Facilities (GB14925-2010). Beijing: China Standard Press; 2011.
17. Xue Kangning, Li Xiaoyan, Rong Rong, et al. Discussion on the management points of experimental activities in the animal biological safety secondary laboratory. Lab Anim Sci. 2014;31:42–45.
18. Abee CR, Mansfield K, Tardif S, et al. Nonhuman Primates in Biomedical Research: Biology and Management. 2nd ed. Washington D.C.: Academic Press; 2012.
19. Scanga Charles A, Lopresti Beian J, Tomko Jaime, et al. In vivo imaging in an ABSL-3 regional biocontainment laboratory. Pathog Dis. 2014;71:207–212.
20. Cheng Shuisheng, Wang Taijian, Xia Yecai, et al. US, Canada biosafety level 3 animal laboratory investigation report. Chin J Vet Med. 2007;41:47–48.