GUIDE
FOR THE CARE AND USE OF
LABORATORY ANIMALS

Eighth Edition

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This eighth edition of the Guide for the Care and Use of Laboratory Animals has been reviewed in draft form by individuals chosen for

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by John Dowling, Harvard University, and John Vandenbergh, North Carolina State University. Appointed by the National Research Council, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

included research scientists, veterinarians, and nonscientists representing biomedical ethics and the public's interest in animal welfare. The Committee widely solicited written and oral comments on the update of the *Guide* from the scientific community and the general public; comments at open meetings (on September 26, 2008, in Washington, DC; October 16, 2008, in Irvine, California; and November 14, 2008, in Chicago) as well as written comments submitted to or requested by the Committee were considered. In addition, the Committee studied the materials submitted to NIH in response to its 2005 Request for Information (NOT-OD-06-011). All comments contributed substantially to this eighth edition of the *Guide*.

In approaching its task, the Committee carried forward the balance between ethical and science-based practice that has always been the basis of the *Guide*, and fulfilled its role to provide an updated resource that enables the research community to proceed responsibly and in a self-regulatory manner with animal experimentation. The *Guide* is predicated on the understanding that the exercise of professional judgment both upholds the central notion of performance standards and obviates the need for more stringent regulations.

Laboratory animal science is a rapidly evolving field and the Committee identified a number of areas in which current available scientific information is insufficient; additional objective information and assessment are needed to provide a scientific basis for recommendations in future editions of the *Guide*. Although pursuing these concepts was beyond this Committee's charge, the following two topics merit further study: (1) space and housing needs of laboratory species and (2) the need and best methods for providing enrichment, exercise, and human contact.

The need for continual updating of the *Guide* is implicit in its objective "to provide information that will enhance animal well-being, the quality of research, and the advancement of scientific knowledge that is relevant to both humans and animals" (Chapter 1). The irregular and increasing intervals between updates, reaching a 14-year gap between the seventh edition and this eighth edition, mean that important new research findings might wait more than a decade before being reflected in recommended practice. Addressing this concern was beyond the charge of this Committee; we noted, however, that regular and more frequent updates of the information in the *Guide* will promote laboratory animal welfare and support high-quality scientific data. A formal process for revising the information in the *Guide*, including the updating of practice standards, could meet this need.

In undertaking this update, the Committee acknowledged the contributions of William I. Gay and Bennett J. Cohen in the development of the original *Guide*. In 1959, Animal Care Panel (ACP) President Cohen appointed the Committee on Ethical Considerations in the Care of Laboratory Animals to evaluate animal care and use. That Committee was chaired by Dr. Gay, who soon recognized that the Committee could not evaluate animal care programs objectively without appropriate criteria on which to base its evaluations—that is, standards were needed. The ACP Executive Committee agreed, and the Professional Standards Committee was appointed. NIH later awarded the ACP a contract to "determine and establish a professional standard for laboratory animal care and facilities." Dr. Cohen chaired the ACP Animal Facilities Standards Committee, which prepared the first *Guide for Laboratory Animal Facilities and Care*.

This edition of the *Guide* was financially supported by the National Institutes of Health; the Office of Research Integrity, Department of Health and Human Services; the US Department of Agriculture (USDA); the Association for Assessment and Accreditation of Laboratory Animal Care International; the American Association for Laboratory Animal Science; Abbott Fund; Pfizer, Inc.; the American College of Laboratory Animal Medicine; the American Society of Laboratory Animal Practitioners; and the Association of Primate Veterinarians.

The Committee for the Update of the *Guide for the Care and Use of Laboratory Animals*

Overview

This eighth edition of the *Guide* is divided into ve chapters and four appendices.

Chapter 1 presents the goals and intended audiences of the *Guide* as well as key concepts and terminology essential to its premise and use. Incorporating some of the material from the Introduction to the last edition, the chapter highlights a commitment to the concepts of the Three Rs—Replacement, Reduction, and Re nement—and provides an enhanced discussion of the ethics of animal use and investigator/institu-tional obligations.

Chapter 2 focuses on the overall institutional animal care and use programpPpter 2 a(s)-3(o)-3(m)-3(e)13(g)-3(ram)-3(e)13(n)-3(n)-3(w-)-3(e)13((n)-3(d) ing the growing role of aquatic animals in biomedical research. The chapter provides recommendations for housing and environment, discusses the importance of social housing, and includes enhanced sections on environmental enrichment, animal well-being, and scientific validity.

Space recommendations were nominally expanded based on the Committee's professional and expert opinion and on current housing methods. Cage sizes have historically been interpreted as minimum space needs by users of the *Guide*, and were labeled as such ("recommended minimum space") in this edition. The use of the word "minimum" does not further restrict users of the *Guide* because, although the space requirements are numbers (i.e., engineering standards), they are used in a performance standards framework. The Committee recommends minimum space for female rodents with litter and an increase of the cage height for rabbits to 16". Further, in light of many comments submitted to the Committee requesting more information on performance goals and how to achieve them, rodent breeding recommendations are accompanied by substantial guidance.

With respect to nonhuman primates (NHPs), the Committee endorses social housing as the default and has provided some species-specific guidance. An additional group has been added for monkeys, and chimpanzees

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Key Concepts

This edition of the Guide for the Care and Use of Laboratory Animals (the Guide) strongly af rms the principle that all who care for, use, or produce animals for research, testing, or teaching must assume responsibility for their well-being. The Guide is created by scientists and veterinarians for scientists and veterinarians to uphold the scienti c rigor and integrity of biomedical research with laboratory animals as expected by their colleagues and society at large.

The Guide plays an important role in decision making regarding the use of vertebrate laboratory animals because it establishes the minimum ethical, practice, and care standards for researchersarding g ginT-3(r)15(c)-3(h)-3(e)

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scope and nature of this responsibility can vary based on the scientific discipline, nature of the animal use, and species involved, but because it affects animal care and use in every situation this responsibility requires that producers, teachers, researchers, and institutions carry out purposeful analyses of proposed uses of laboratory animals. The *Guide* is central to these analyses and to the development of a program in which humane care is incorporated into all aspects of laboratory animal care and use.

APPLICABILITY AND GOALS

In the *Guide*, *laboratory animals* (also referred to as *animals*) are generally defined as any vertebrate animal (i.e., traditional laboratory animals, agricultural animals, wildlife, and aquatic species) produced for or used in research, testing, or teaching. *Animal use* is defined as the proper care, use, and humane treatment of laboratory animals produced for or used in research, testing, or teaching.

> Laboratory animals or animals: Any vertebrate animal (e.g., traditional laboratory animals, agricultural animals, wildlife, and aquatic species) produced for or used in research, testing, or teaching.

When appropriate, considerations or specific emphases for agricultural animals and nontraditional species are presented. The *Guide* does not address in detail agricultural animals used in production, agricultural research or teaching, wildlife and aquatic species studied in natural settings, or invertebrate animals (e.g., cephalopods) used in research, but establishes general principles and ethical considerations that are also applicable to these species and situations. References provide the reader with additional resources, and supplemental information on breeding, care, management, and use of selected laboratory animal species is available in other publications prepared by the Institute for Laboratory Animal Research (ILAR) and other organizations (Appendix A).

> Animal use: The proper care, use, and humane treatment of laboratory animals produced for or used in research, testing, or teaching.

The goal of the *Guide* is to promote the humane care and use of laboratory animals by providing information that will enhance animal well-being, the quality of research, and the advancement of scientific knowledge that is relevant to both humans and animals. The Committee recognizes that the use of different species in research is expanding and that researchers and institutions will face new and unique challenges in determining how to apply the *Guide* in these situations. In making such determinations, it is important to keep in mind that the Guide is intended to provide information to assist researchers, institutional animal care and use committees (IACUCs), veterinarians, and other stakeholders in ensuring the implementation of effective and appropriate animal care and use programs that are based on humane care. Throughout the Guide, scientists and institutions are encouraged to give careful and deliberate thought to the decision to use animals, taking into consideration the contribution that such use will make to new knowledge, ethical concerns, and the availability of alternatives to animal use (NRC 1992). A practical strategy for decision making, the “Three Rs” (Replacement, Reduction, and Refinement) approach, is discussed in more detail below. Institutions should use the recommendations in the Guide as a foundation for the development of a comprehensive animal care and use program and a process for continually improving this program.

INTENDED AUDIENCES AND USES OF THE GUIDE

The Guide is intended for a wide and diverse audience, including

- the scientific community
- administrators
- IACUCs
- veterinarians
- educators and trainers
- producers of laboratory animals
- accreditation bodies
- regulators
- the public.

The Guide is meant to be read by the user in its entirety, as there are valuable for their oversight and support of animal care and use. Educators and trainers can use the *Guide* as a document to assess both the scope and adequacy of training programs supported by the institution. Accreditation bodies will find the *Guide* useful for evaluating many areas of animal care and use programs not subject to strict engineering standards (see definition below). Finally, members of the public should feel assured that adherence to the *Guide* will ensure humane care and use of laboratory animals.

Readers are reminded that the *Guide* is used by a diverse group of national and international institutions and organizations, many of which are covered by neither the Animal Welfare Act nor the PHS Policy. The *Guide* uses some terminology that is both defined by US statute and denotes a general concept (e.g., "attending veterinarian," "adequate veterinary care," and "institutional official"). Even if these terms are not consistent with those used by non-US institutions, the underlying principles can still be applied. In all instances where *Guide* recommendations are different from applicable legal or policy requirements, the higher standard should apply.

ETHICS AND ANIMAL USE

The decision to use animals in research requires critical thought, judgment, and analysis. Using animals in research is a privilege granted by society to the research community with the expectation that such use will provide either significant new knowledge or lead to improvement in human and/or animal well-being (McCarthy 1999; Perry 2007). It is a trust that mandates responsible and humane care and use of these animals. The *Guide* endorses the responsibilities of investigators as stated in the *U.S. Government Principles for Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* (IRAC 1985; see Appendix B). These principles direct the research community to accept responsibility for the care and use of animals during all phases of the research effort. Other government agencies and professional organizations have published similar principles (NASA 2008; NCB 2005; NIH 2006, 2007; for additional references see Appendix A). Ethical considerations discussed here and in other sections of the *Guide* should serve as a starting design in laboratory animal research (Russell and Burch 1959). Over the years, the Three Rs have become an internationally accepted approach for researchers to apply when deciding to use animals in research and in designing humane animal research studies.

Replacement refers to methods that avoid using animals. The term includes absolute replacements (i.e., replacing animals with inanimate systems such as computer programs) as well as relative replacements (i.e., replacing animals such as vertebrates with animals that are lower on the phylogenetic scale).

Re nement refers to modi cations of husbandry or experimental prored(p)-3(e)-(

Humane Care

Humane care means those actions taken to ensure that laboratory animals are treated according to high ethical and scienti c standards. Implementation of a humane care program, and creation of a laboratory environment in which humane care and respect for animals are valued and encouraged, underlies the core requirements of the *Guide* and the system expertise, and research goals) so that implementation can be best tailored to meet the recommendations in the *Guide*.

Ideally, engineering and performance standards are balanced, setting a target for optimal practices, management, and operations while encouraging flexibility and judgment, if appropriate, based on individual situations (Gonder et al. 2001).

Scientists, veterinarians, technicians, and others have extensive experience and information covering many of the topics discussed in the *Guide*. For topics on which information is insufficient or incomplete, sustained research into improved methods of laboratory animal management, care, and use is needed for the continued evaluation and improvement of performance and engineering standards.

Practice standard means the application of professional judgment by qualified, experienced individuals to a task or process over time, an approach that has been demonstrated to benefit or enhance animal care and use. Professional judgment comes from information in the peer-reviewed scientific literature and textbooks and, as in many other disciplines, from time-proven experiences in the field (for additional information see Chapter 2). In the absence of published scientific literature or other definitive sources, where experience has demonstrated that a particular practice improves animal care and use, practice standards have been used in determining appropriate recommendations in the *Guide*. In most situations, the *Guide* is intended to provide flexibility so that institutions can modify practices and procedures with changing conditions and new information.

POLICIES, PRINCIPLES, AND PROCEDURES

Policies commonly derive from a public agency or private entity. They are generally practical statements of collective wisdom, convention, or management direction that are internal to the entity. However, policies may assume broader force when they become the means by which an implementing agency interprets existing statutes (e.g., *PHS Policy*). *Principles* are broader in their scope and intended application, and are accepted generalizations about a topic that are frequently endorsed by many and diverse organizations (e.g., the *U.S. Government Principles*). *Procedures* (often called “operating procedures” or “standard operating procedures”) are typically detailed, step-by-step processes meant to ensure the consistent application of institutional practices. Establishing standard operating proce-

MUST, SHOULD, AND MAY

Must indicates actions that the Committee for the Update of the *Guide* considers imperative and mandatory duty or requirement for providing humane animal care and use. *Should* indicates a strong recommendation for achieving a goal; however, the Committee recognizes that individual circumstances might justify an alternative strategy. *May* indicates a suggestion to be considered.

The *Guide* is written in general terms so that its recommendations can be applied in diverse institutions and settings that produce or use animals for research, teaching, and testing. This approach requires that users, IACUCs, veterinarians, and producers apply professional judgment in making speci c

2

Animal Care and Use Program

The proper care and use of laboratory animals in research, testing, teaching, and production (animal use) require scientific and professional judgment based on the animals' needs and their intended use. An animal care and use program (hereafter referred to as the Program) comprises all activities conducted by and at an institution that have a direct impact on the well-being of animals, including animal and veterinary care, policies and procedures, personnel and program management and oversight, occupational health and safety, institutional animal care and use committee (IACUC) functions, and animal facility design and management.

> Program: The activities conducted by and at an institution that have a direct impact on the well-being of animals, including animal and veterinary care, policies and procedures, personnel and program management and oversight, occupational health and safety, IACUC functions, and animal facility design and management.

This chapter defines the overall Program and key oversight responsibilities and provides guidelines to aid in developing an effective Program. Chapters 3, 4, and 5 cover the details of Program components: environment, housing, and management; veterinary care; and physical plant, respectively. Each institution should establish and provide sufficient resources for a Program that is managed in accord with the *Guide* and in compliance with applicable regulations, policies, and guidelines.

REGULATIONS, POLICIES, AND PRINCIPLES

The use of laboratory animals is governed by an interrelated, dynamic of literature related to animal science and use of animals is constantly evolving, requiring Programs to remain current with the information and best practices.

PROGRAM MANAGEMENT

An effective Program requires clearly defined roles that align responsibility with regulatory and management authority. US federal law creates a statutory basis for the institutional official (IO), the attending veterinarian (AV), and the institutional animal care and use committee (IACUC). The *Guide* endorses these concepts as important operating principles for all US and non-US animal care and use programs. Effective leadership in and collaboration among these three components, which not only oversee but also support animal users, are necessary (Lowman 2008; Van Sluyters 2008). In addition, interactions with regulatory and funding agencies and accreditation organizations are an integral part of the Program.

As summarized here and discussed throughout the *Guide*, the primary oversight responsibilities in the Program rest with the IO, the AV, and the IACUC. Their roles fit in a defined organizational structure where the reporting relationships, authorities, and responsibilities of each are clearly defined and transparent. Together they establish policies and procedures, ensure regulatory compliance, monitor Program performance, and support high-quality science and humane animal use. A Program that includes these elements and establishes a balance among them has the best chance of efficiently using resources while attaining the highest standards of animal well-being and scientific quality (Bayne and Garnett 2008; Van Sluyters 2008).

Program Management Responsibility

The Institutional Official

The institutional official (IO) bears ultimate responsibility for the Program, although overall Program direction should be a shared responsibility among the IO, AV, and IACUC. The IO has the authority to allocate the resources needed to ensure the Program's overall effectiveness. Program needs should be clearly and regularly communicated to the IO by the AV, the IACUC, and others associated with the Program (e.g., facilities management staff, occupational health and safety personnel, scientists). As a

> Institutional official: The individual who, as a representative of senior administration, bears ultimate responsibility for the Program and is responsible for resource planning and ensuring alignment of Program goals with the institution's mission.

animal science and medicine are rapidly changing and evolving disciplines. The institution should provide opportunities and support for regular professional development and continuing education to ensure both that professional staff are knowledgeable about the latest practices and procedures and that laboratory animals receive high-quality care (Colby et al. 2007).

Animal Care Personnel Personnel caring for animals should be appropriately trained (see Appendix A, Education), and the institution should provide for formal and/or on-the-job training to facilitate effective implementation of the Program and the humane care and use of animals. Staff should receive training and/or have the experience to complete the tasks for which they are responsible. According to the Program scope, personnel with expertise in various disciplines (e.g., animal husbandry, administration, veterinary medical technology) may be required.

There are a number of options for training animal care personnel and technicians (Pritt and Duffee 2007). Many colleges have accredited programs in veterinary technology (AVMA 2010); most are 2-year programs that award Associate of Science degrees, some are 4-year programs that award Bachelor of Science degrees. Nondegree training, via certi cation used (Conarello and Shepard 2007). Training should be tailored to the particular needs of research groups; however, all research groups should receive training in animal care and use legislation, IACUC function, ethics of animal use and the concepts of the Three Rs, methods for reporting concerns about animal use, occupational health and safety issues pertaining to animal use, animal handling, aseptic surgical technique, anesthesia and analgesia, euthanasia, and other subjects, as required by statute. Continuing education programs should be offered to reinforce training and provide updates that re ect changes in technology, legislation, and other relevant areas. Frequency of training opportunities should ensure that all animal there is a regulatory requirement for such a committee. Operational and day-to-day responsibility for safety in the workplace resides with the laboratory or facility supervisor (e.g., principal investigator, facility director, or a staff veterinarian) and depends on safe work practices by all employees.

Control and Prevention Strategies A comprehensive OHSP should include a hierarchy of control and prevention strategies that begins with the identification of hazards and the assessment of risk associated with those hazards. Managing risk involves the following steps: first, the appropriate design and operation of facilities and use of appropriate safety equipment (engineering controls); second, the development of processes and standard operating procedures (SOPs; administrative controls); and finally, the provision of appropriate personal protective equipment (PPE) for employees. Special safety equipment should be used in combination with appropriate management and safety practices (NIH 2002; OSHA 1998a,b). Managing risk using these strategies requires that personnel be trained, maintain good personal hygiene, be knowledgeable about the hazards in their work environment, understand the proper selection and use of equipment, follow established procedures, and use the PPE provided.

Hazard Identification and Risk Assessment The institutional OHSP should identify potential hazards in the work environment and conduct a critical assessment of the associated risks. An effective OHSP ensures that the risks associated with the experimental use of animals are identified and reduced to minimal and acceptable levels. Hazard identification and risk assessment are ongoing processes that involve individuals qualified to assess dangers associated with the Program and implement commensurate safeguards. Health and safety specialists with knowledge in relevant disciplines should be involved in risk assessment and the development of procedures to manage such risks.

Potential hazards include experimental hazards such as biologic agents (e.g., infectious agents or toxins), chemical agents (e.g., carcinogens and mutagens), radiation (e.g., radionuclides, X-rays, lasers), and physical hazards (e.g., needles and syringes). The risks associated with unusual experimental conditions such as those encountered in field studies or wildlife research should also be addressed. Other potential hazards—such as animal bites, exposure to allergens, chemical cleaning agents, wet floors, cage washers and other equipment, lifting, ladder use, and zoonoses—that are inherent in or intrinsic to animal use should be identified and evaluated. Once potential hazards have been identified, a critical ongoing assessment of the associated risks should be conducted to determine appropriate strategies to minimize or manage the risks.

The extent and level of participation of personnel in the OHSP should be based on the hazards posed by the animals and materials used (the severity or seriousness of the hazard); the exposure intensity, duration, and frequency (prevalence of the hazard); to some extent, the susceptibility (e.g., immune status) of the personnel; and the history of occupational illness and injury in the particular workplace (Newcomer 2002; NRC 1997). Ongoing identification and evaluation of hazards call for periodic inspections and reporting of potential hazardous conditions or “near miss” incidents.

Facilities, Equipment, and Monitoring The facilities required to support the OHSP will vary depending on the scope and activities of the Program. Their design should preferentially use engineering controls and equipment to minimize exposure to anticipated hazards (also see Chapter 5). Because a high standard of personal cleanliness is essential, changing, washing, and showering facilities and supplies appropriate to the Program should be available.

Where biologic agents are used, the Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH) publication *Biosafety in Microbiological and Biomedical Laboratories* (BMBL; DHHS 2009) and the USDA standards (USDA 2002) should be consulted for appropriate facility design and safety procedures. These design and safety features are based on the level of risk posed by the agents used. Special facilities and safety equipment may be needed to protect the animal care and investigative staff, other occupants of the facility, the public, animals, and the environment from exposure to hazardous biologic, chemical, and physical agents used in animal experimentation (DHHS 2009; Frasier and Talka 2005; NIH 2002). When necessary, these facilities should be separated from other animal housing and support areas, research and clinical laboratories, and patient care facilities. They should be appropriately identified and access to them limited to authorized personnel.

Facilities, equipment, and procedures should also be designed, selected, and developed to reduce the possibility of physical injury or health risk to personnel (NIOSH 1997a,b). Engineering controls and equipment that address the risk of ergonomic injury in activities such as the lifting of heavy equipment or animals should be considered (AVMA 2008). Those are also frequently used to limit or control personnel exposure to animal allergens (Harrison 2001; Huerkamp et al. 2009). The potential for repetitive motion injuries in animal facilities (e.g., maintenance of large rodent populations and other husbandry activities) should also be assessed.

The selection of appropriate animal housing systems requires professional knowledge and judgment and depends on the nature of the hazards in question, the types of animals used, the limitations or capabilities of the facilities, and the design of the experiments. Experimental animals should be housed so that possibly contaminated food and bedding, feces, and urine

Institutions should have written policies and procedures governing experimentation with hazardous biologic, chemical, and physical agents. An oversight process (such as the use of a safety committee) should be developed to involve persons who are knowledgeable in the evaluation and safe use of hazardous materials or procedures and should include review of the procedures and facilities to be used for speci c safety concerns. Formal safety programs should be established to assess hazards, determine the safeguards needed for their control, and ensure that staff have the necessary training and skills and that facilities are adequate for the safe conduct of the research. Technical support should be provided to monitor and ensure compliance with institutional safety policies. A collaborative approach involving the investigator and research team, attending veterinarian, animal care technician, and occupational health and safety professionals may enhance compliance.

The BMBL (DHHS 2009) and NRC (1997) recommend practices and procedures, safety equipment, and facility requirements for working with hazardous biologic agents and materials. Facilities that handle agents of unknown risk should consult with appropriate CDC personnel about hazard control and medical surveillance. The use of highly pathogenic “select agents and toxins” in research requires that institutions develop a program and procedures for procuring, maintaining, and disposing of these agents (CFR 1998, 2002a,b; NRC 2004; PL 107-56; PL 107-188; Richmond et al. 2003). The use of immunode cient or genetically modi ed animals (GMAs) susceptible to or shedding human pathogens, the use of human tissues and cell lines, or any infectious disease model can lead to an increased risk to the health and safety of personnel working with the animals (Lassnig et al. 2005; NIH 2002).

Hazardous agents should be contained in the study environment, for example through the use of air ow control during the handling and administering of hazardous agents, necropsies on contaminated animals (CDC and NIH 2000), and work with chemical hazards (Thomann 2003). Waste anesthetic gases should be scavenged to limit exposure.

Personal Protection While engineering and administrative controls are the as gloves, arm protectors, suitable face masks, face shields, and goggles (NRC 2003a). Hearing protection should be available in high-noise areas (OSHA 1998c). Personnel working in areas where they might be exposed to contaminated airborne particulate material or vapors should have suitable respiratory protection (Fechter 1995; McCullough 2000; OSHA 1998d), with respirator fit testing and training in the proper use and maintenance of the respirator (OSHA 1998d; Sargent and Gallo 2003).

Medical Evaluation and Preventive Medicine for Personnel Development and implementation of a program of medical evaluation and preventive medicine should involve input from trained health professionals, such as occupational health physicians and nurses. Confidentiality and other medical and legal factors must be considered in the context of appropriate federal, state, and local regulations (e.g., PL 104-191).

A preemployment health evaluation and/or a health history evaluation before work assignment is advisable to assess potential risks for individual employees. Periodic medical evaluations are advisable for personnel in specific risk categories. For example, personnel required to use respiratory protection may also require medical evaluation to ensure that they

employee(s), unless such concerns are reported anonymously; corrective actions if deemed necessary; and a report to the IO of the issue, findings, and actions taken. Reported concerns and any corrective actions taken should be documented.

Mechanisms for reporting concerns should be posted in prominent locations in the facility and on applicable institutional website(s) with instructions on how to report the concern and to whom. Multiple points of contact, including senior management, the IO, IACUC Chair, and AV, are recommended. The process should include a mechanism for anonymity, compliance with applicable whistleblower policies, nondiscrimination against the concerned/reporting party, and protection from reprisals.

Training and regular communication with employees (including personnel such as custodial, maintenance, and administrative staff, who are farther removed from the animal use) about the institution's animal use activities may reduce potential concerns.

PROGRAM OVERSIGHT

The Role of the IACUC

IACUC Constitution and Function

The responsibility of the IACUC is to oversee and routinely evaluate the Program. It is the institution's responsibility to provide suitable orientation, background materials, access to appropriate resources, and, if necessary, specific training to assist IACUC members in understanding their roles and responsibilities and evaluating issues brought before the committee.

Committee membership includes the following:

- a Doctor of Veterinary Medicine either certified (e.g., by ACLAM, ECLAM, JCLAM, KCLAM) or with training and experience in laboratory animal science and medicine or in the use of the species at the institution
- at least one practicing scientist experienced in research involving animals
- at least one member from a nonscientific background, drawn from inside or outside the institution
- at least one public member to represent general community interests in the proper care and use of animals.

Public members should not be laboratory animal users, affiliated in any way with the institution, or members of the immediate family of a person who is affiliated with the institution. The public member may receive compensation for participation and ancillary expenses (e.g., meals, parking, travel), but the amount should be sufficiently modest that it does not become a substantial source of income and thus risk compromising the member's association with the community and public at large.

For large institutions with many administrative units or departments, no more than three voting members should be associated with a single administrative unit (USDA 1985). The size of the institution and the nature and extent of the Program will determine the number of members of the committee and their terms of appointment. Institutions with broad research programs may need to choose scientists from a number of disciplines and experience to properly evaluate animal use protocols.

The committee is responsible for oversight and evaluation of the entire Program and its components as described in other sections of the *Guide*. Its oversight functions include review and approval of proposed animal use (protocol review) and of proposed significant changes to animal use; regular inspection of facilities and animal use areas; regular review of the Program; ongoing assessment of animal care and use; and establishment of a mechanism for receipt and review of concerns involving the care and use of animals at the institution. The committee must meet as often as necessary to fulfill its responsibilities, and records of committee meetings and results of deliberations should be maintained. Program review and facilities inspections should occur at least annually or more often as required (e.g., by the Animal Welfare Act and PHS Policy). After review and inspection, a written report (including any minority views) should be provided to the IO about the status of the Program.

Protocol Review

The animal use protocol is a detailed description of the proposed use of laboratory animals. The following topics should be considered in the preparation of the protocol by the researcher and its review by the IACUC:

- rationale and purpose of the proposed use of animals
- a clear and concise sequential description of the procedures involving the use of animals that is easily understood by all members of the committee
- availability or appropriateness of the use of less invasive procedures, other species, isolated organ preparation, cell or tissue culture, or computer simulation (see Appendix A, Alternatives)
- justification of the species and number of animals proposed; whenever possible, the number of animals and experimental group sizes should be statistically justified (e.g., provision of a power analysis; see Appendix A, Experimental Design and Statistics)

- unnecessary duplication of experiments

Special Considerations for IACUC Review

Certain animal use protocols include procedures or approaches that require special consideration during the IACUC review process due to their potential for unrelieved pain or distress or other animal welfare concerns. The topics below are some of the most common requiring special IACUC consideration. For these and other areas the IACUC is obliged to weigh the objectives of the study against potential animal welfare concerns. By considering opportunities for re nement, the use of appropriate nonanimal alternatives, and the use of fewer animals, both the institution and the principal investigator (PI) can begin to address their shared obligations for humane animal care and use.

Experimental and Humane EndpointsThe experimental endpoint of a study occurs when the scienti c aims and objectives have been reached. The humane endpoint is the point at which pain or distress in an experimental animal is prevented, terminated, or relieved. The use of humane endpoints contributes to re nement by providing an alternative to experimental end-

cbj a(o)-3(n)-3(t)-3(l)-3(t)-3((o)-3a)-3(le)-3(r)-3(o)110(v)-3(e)-3(nx)-3krdro())-3Werl nd2 humane endpoint, and the response required upon reaching the humane endpoint. An understanding of preemptive euthanasia (Toth 2000), behavioral or physiologic de nitions of the moribund state (ibid.), and the use of study-speci c animal assessment records (Morton 2000; Paster et al. 2009) can aid the PI and IACUC when considering or developing proposed endpoints. When novel studies are proposed or information for an alternative endpoint is lacking, the use of pilot studies is an effective method for identifying and de ning humane endpoints and reaching consensus among the PI, IACUC, and veterinarian. A system for communication with the IACUC should be in place both during and after such studies. Numerous publications address speci c proposals for the application and use of humane endpoints (e.g., CCAC 1998; ILAR 2000; OECD 1999; Toth 1997; UKCCCR 1997).

Unexpected Outcomes Fundamental to scienti c inquiry is the investigation of novel experimental variables. Because of the potential for unexpected outcomes that may affect animal well-being when --217f-3(a)-3(l)-3( )-h3(-

help to determine whether proactive measures can circumvent or alleviate the impact of the genetic modi cation on the animal's well-being and to establish humane endpoints speci c to the GMA line.

Physical Restraint Physical restraint is the use of manual or mechanical means to limit some or all of an animal's normal movement for the purpose of examination, collection of samples, drug administration, therapy, or experimental manipulation. Animals are restrained for brief periods, usually minutes, in many research applications.

Restraint devices should be suitable in size, design, and operation to minimize discomfort, pain, distress, and the potential for injury to the animal and the research staff. Dogs, nonhuman primates, and many other animals can be trained, through use of positive reinforcement techniques, to cooperate with research procedures or remain immobile for brief periods (Boissy et al. 2007; Laule et al. 2003; Meunier 2006; Prescott and Buchanan-Smith 2003; Reinhardt 1991, 1995; Sauceda and Schmidt 2000; Yeates and Main 2009).

Prolonged restraint, including chairing of nonhuman primates, should be avoided unless it is essential for achieving research objectives and is speci cally approved by the IACUC (NRC 2003b). Systems that do not limit an animal's ability to make normal postural adjustments (e.g., subcutaneous implantation of osmotic minipumps in rodents, backpack- tted infusion pumps in dogs and nonhuman primates, and free-stall housing for

(t)-3(m)-3(e)-3(n)-3(t)-3(s)-3( )-149(()-3(e(c)-3(u)-4(u)-4(u)-4(u)-(g)-3( )-pp)-3(r)-3(o)-3
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- Veterinary care must be provided if lesions or illnesses associated with restraint are observed. The presence of lesions, illness, or severe behavioral change often necessitates the temporary or permanent removal of the animal from restraint.
- The purpose of the restraint and its duration should be clearly explained to personnel involved with the study.

Multiple Survival Surgical Procedures Surgical procedures in the laboratory setting may be categorized as major or minor (USDA 1985). Whether a procedure is major or minor should be evaluated on a case-by-case basis, as determined by the veterinarian and IACUC (NRC 2003b; Silverman et al. 2007; for additional discussion see Chapter 4, Surgical Procedures).

Regardless of classi cation, multiple surgical procedures on a single animal should be evaluated to determine their impact on the animal's well-being. Multiple major surgical procedures on a single animal are acceptable only if they are (1) included in and essential components of a single research project or protocol, (2) scienti cally justi ed by the investigator, or (3) necessary for clinical reasons. Conservation of scarce animal resources may justify the conduct of multiple major surgeries on a single animal, but the application of such a practice on a single animal used in separate protocols is discouraged and should be reviewed critically by the IACUC. When applicable, the IO must submit a reQsw40 [(()-3()-3(O)-3( )-112(m)-3(u)-3(Dtg least restriction necessary to achieve the scientific objective while maintaining animal well-being.

The development of animal protocols that involve the use of food or fluid regulation requires the evaluation of three factors: the necessary level of regulation, potential adverse consequences of regulation, and methods for assessing the health and well-being of the animals (NRC 2003b). In addition, the following factors influence the amount of food or fluid restriction that can be safely used in a specific protocol: the species, strain, or stock, gender, and age of the animals; thermoregulatory demand; type of housing; time of feeding, nutritive value, and fiber content of the diet (Heiderstadt et al. 2000; Rowland 2007); and prior experimental manipulation. The degree of food or fluid restriction necessary for consistent behavioral performance is influenced by the difficulty of the task, the individual animal, the motivation required of the animal, and the effectiveness of animal training for a specific protocol-related task.

The animals should be closely monitored to ensure that food and fluid intake meets their nutritional needs (Toth and Gardiner 2000). Body weights should be recorded at least weekly and more often for animals requiring greater restrictions (NRC 2003b). Written records should be maintained for each animal to document daily food and fluid consumption, hydration status, and any behavioral and clinical changes used as criteria for temporary or permanent removal of an animal from a protocol (Morton 2000; NRC 2003b). In the case of conditioned-response research protocols, use of a highly preferred food or fluid as positive reinforcement, instead of restriction, is recommended. Caloric restriction, as a husbandry technique and means of weight control, is discussed in Chapter 3.

Use of Non-Pharmaceutical-Grade Chemicals and Other Substances The

Field Investigations Investigations may involve the observation or use of nondomesticated vertebrate species under eld conditions. Many eld investigations require international, federal, state, and/or local permits, which may call for an evaluation of the scienti c merit of the proposed study and a determination of the potential impact on the population or species to be studied.

Additionally, occupational health and safety issues, including zoonoses, should be reviewed by the institution's health and safety committee or of ce, with assurances to the IACUC that the eld study does not compromise the health and safety of either animals or persons in the eld. Principal investigators conducting eld research should be knowledgeable about relevant zoonotic diseases, associated safety issues, and any laws or regulations that apply. Exceptions to the above should be clearly de ned and evaluated by the IACUC.

In preparing the design of a eld study, investigators are encouraged to consult with relevant professional societies and available guidelines (see Appendix A). Veterinary input may be needed for projects involving capture, individual identi cation, sedation, anesthesia, surgery, recovery, holding, transportation, release, or euthanasia. Issues associated with these activities are similar if not identical to those for species maintained and used in the laboratory. When species are removed from the wild, the protocol should include plans for either a return to their habitat or their nal disposition, as appropriate.

The Guide does not purport to be a compendium of all information regarding eld biology and methods used in wildlife investigations, but the basic principles of humane care and use apply to animals living under natural conditions. IACUCs engaged in the review of eld studies are encouraged to consult with a quali ed wildlife biologist.

Agricultural Animals The use of agricultural animals in research is subject to the same ethical considerations as for other animals in research, although it is often categorized as either biomedical or agricultural because of government regulations and policies, institutional policies, administrative structure, funding sources, and/or user goals (Stricklin et al. 1990). This categorization has led to a dual system with different criteria for evaluating protocols and standards of housing and care for animals of the same species on the basis of stated biomedical or agricultural research objectives (Stricklin and Mench 1994). With some studies, differences in research goals may lead to a clear distinction between biomedical and agricultural research. For example, animal models of human diseases, organ transplantation, and major surgery are considered biomedical u fd disease studies, administrators, regulators, and IACUCs face a dilemma in deciding how to handle such studies (Stricklin et al. 1990). Decisions on categorizing research uses of agricultural animals and defining standards for their care and use should be made by the IACUC based on both the researcher's goals and concern for animal well-being. Regardless of the category of research, institutions are expected to provide oversight of all research animals and ensure that pain and distress are minimized.

The protocol, rather than the category of research, should determine the setting (farm or laboratory). Housing systems for agricultural animals used in biomedical research may or may not differ from those used in agricultural research; animals used in either type of research can be housed in cages, stalls, paddocks, or pastures (Tillman 1994). Some agricultural studies need uniform conditions to minimize environmental variability, and some biomedical studies are conducted in farm settings. Agricultural research often necessitates that animals be managed according to contemporary farm production practices (Stricklin and Mench 1994), and natural environmental conditions might be desirable for agricultural research, whereas control of environmental conditions to minimize variation might be desirable in biomedical research (Tillman 1994).

The *Guide* applies to agricultural animals used in biomedical research, including those maintained in typical farm settings. For animals maintained in a farm setting, the *Guide for the Care and Use of Agricultural Animals in Research and Teaching* (FASS 2010) is a useful resource. Information about environmental enrichment, transport, and handling may be helpful in both agricultural and biomedical research settings. Additional information about facilities and management of farm animals in an agricultural setting is available from the Midwest Plan Service (1987) and from agricultural engineers or animal science experts.

Postapproval Monitoring

Continuing IACUC oversight of animal activities is required by federal laws, regulations, and policies. A variety of mechanisms can be used to facilitate ongoing protocol assessment and regulatory compliance. Postapproval monitoring (PAM) is considered here in the broadest sense, consist-ments. The IACUC, veterinary, animal care, and compliance staff may all conduct PAM, which may also serve as an educational tool.

Continuing protocol review typically consists of an annual update or review as well as the triennial review required by the PHS. The depth of such reviews varies from a cursory update to a full committee review of the entire protocol. Some institutions use the annual review as an opportunity for the investigator to submit proposed amendments for future procedures, to provide a description of any adverse or unanticipated events, and to provide updates on work progress. For the triennial review, many institutions require a complete new protocol submission and may request a progress report on the use of animals during the previous 3 years.

Both the Health Research Extension Act and the AWA require the IACUC to inspect animal care and use facilities, including sites used for animal surgeries, every 6 months. As part of a formal PAM program some institutions combine inspection of animal study sites with concurrent review of animal protocols. Based on risks to animals and their handlers, other study areas may require more or less frequent inspections. Examples of effective monitoring strategies include

- examination of surgical areas, including anesthetic equipment, use of appropriate aseptic technique, and handling and use of controlled substances
- review of protocol-related health and safety issues
- review of anesthetic and surgical records
- regular review of adverse or unexpected experimental outcomes affecting the animals
- observation of laboratory practices and procedures and comparison with approved protocols.

Institutions may also consider the use of veterinary staff and/or animal health technicians to observe increased risk procedures for adverse events (e.g., novel survival surgeries, pain studies, tumor growth studies) and report their findings for review by the IACUC. The level of formality and intensity of PAM should be tailored to institutional size and complexity, and in all cases should support a culture of care focusing on the animals' well-being (Klein and Bayne 2007). Regardless of the methods used or who conducts and coordinates the monitoring, PAM programs are more likely to succeed when the institution encourages an educational partnership with investigators (Banks and Norton 2008; Collins 2008; Dale 2008; Lowman 2008; Plante and James 2008; Van Sluyters 2008).

DISASTER PLANNING AND EMERGENCY PREPAREDNESS

Animal facilities may be subject to unexpected conditions that result in the catastrophic failure of critical systems or significant personnel absenteeism, or other unexpected events that severely compromise ongoing animal care and well-being (ILAR 2010). Facilities must therefore have a disaster plan. The plan should define the actions necessary to prevent animal pain, distress, and deaths due to loss of systems such as those that control ventilation, cooling, heating, or provision of potable water. If possible the plan should describe how the facility will preserve animals that are necessary for critical research activities or are irreplaceable. Knowledge of the geographic locale may provide guidance as to the probability of a particular type of disaster.

Disaster plans should be established in conjunction with the responsible investigator(s), taking into consideration both the priorities for triaging animal populations and the institutional needs and resources. Animals that cannot be relocated or protected from the consequences of the disaster must be humanely euthanized. The disaster plan should identify essential personnel who should be trained in advance in its implementation. Efforts should be taken to ensure personnel safety and provide access to essential personnel during or immediately after a disaster. Such plans should be approved by the institution and be part of the overall institutional disaster response plan that is coordinated by the IO or another senior-level administrator. Law enforcement and emergency personnel should be provided with a copy of the plan for comment and integration into broader, areawide planning (Vogelweid 1998).

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reptiles and certain amphibian species, are terrestrial. Personnel working with aquatic animals should be familiar with management implications, e.g., the importance of providing appropriate temperature ranges for basic physiologic function.

TERRESTRIAL ANIMALS

Terrestrial Environment

Microenvironment and Macroenvironment

The microenvironment of a terrestrial animal is the physical environment immediately surrounding it; that is, the primary enclosure such as the cage, pen, or stall. It contains all the resources with which the animals come directly in contact and also provides the limits of the animals' immediate environment. The microenvironment is characterized by many factors, including illumination, noise, vibration, temperature, humidity, and gaseous and particulate composition of the air. The physical environment of the secondary enclosure, such as a room, a barn, or an outdoor habitat, constitutes themacroenvironment.

> Microenvironment: The immediate physical environment surrounding the animal (i.e., the environment in the primary enclosure such as the cage, pen, or stall).

> Macroenvironment: The physical environment of the second
> factors, int

Temperature and Humidity

environmental relative humidity may be of greater importance for animals housed in a primary enclosure in which the environmental conditions differ greatly from those of the macroenvironment (e.g., in static lter-top [isola tor] cages).

Some species may require conditions with high relative humidity (e.g., and should therefore be considered. The use of computer modeling for assessing those factors in relation to heat loading, air diffusion patterns, and particulate movement may be helpful in optimizing ventilation of micro- and macroenvironments (Hughes and Reynolds 1995).

Direct exposure of animals to air moving at high velocity (drafts) should be avoided as the speed of air to which animals are exposed affects the rate at which heat and moisture are removed from an animal. For example, air at 20°C moving at 60 linear feet per minute (18.3 m/min) has a cooling effect of approximately 7°C (Weihe 1971). Drafts can be particularly problematic for neonatal homeotherms (which may be hairless and have poorly developed mechanisms for thermoregulatory control), for mutants lacking fur, and for semiaquatic amphibians that can desiccate.

Provision of 10 to 15 fresh air changes per hour in animal housing rooms is an acceptable guideline to maintain macroenvironmental air quality by constant volume systems and may also ensure microenvironmental air quality. Although this range is effective in many animal housing settings, it does not take into account the range of possible heat loads; the species, size, and number of animals involved; the type of primary enclosure and bedding; the frequency of cage changing; the room dimensions; or the ef-ciency of air distribution both in the macroenvironment and between the macro- and microenvironments. In some situations, the use of such a broad guideline might overventilate a macroenvironment containing few animals, thereby wasting energy, or underventilate a microenvironment containing many animals, allowing heat, moisture, and pollutants to accumulate.

Modern heating, ventilation, and air conditioning (HVAC) systems (e.g., variable air volume, or VAV, systems) allow v1(u)-3(n)-3(d)-3(e)-3(r)-3(v)-3(e)-3(n)-3 able to exhaust these systems directly into the building's exhaust system to reduce heat load and macroenvironmental contamination.

well as the duration of the animal's current and prior exposure to light, and the animal's pigmentation, circadian rhythm, body temperature, hormonal status, age, species, sex, and stock or strain (Brainard 1989; Duncan and O'Steen 1985; O'Steen 1980; Saltarelli and Coppola 1979; Semple-Rowland and Dawson 1987; Wax 1977). More recent studies in rodents and primates have shown the importance of intrinsically photosensitive retinal ganglion cells (distinct from rods and cones) for neuroendocrine, circadian, and neurobehavioral regulation (Berson et al. 2002; Hani n and Brainard 2007). These cells can respond to light wavelengths that may differ from other photoreceptors and may in uence the type of lighting, light intensity, and wavelength selected for certain types of research.

In general, lighting should be diffused throughout an animal holding area and provide suf cient illumination for the animals' well-being while permitting good housekeeping practices, adequate animal inspection midcage (NASA 1988). Rats and mice generally prefer cages with low light intensity (Blom et al. 1996), and albino rats prefer areas with a light intensity of less than 25 lux (Schlingmann et al. 1993a). Young mice prefer much lower illumination than adults (Wax 1977). For animals that have been shown to be susceptible to phototoxic retinopathy, light should be between 130 and 325 lux in the room at cage level.

Light intensity decreases with the square of the distance from its source. Thus the location of a cage on a rack affects the intensity of light to which the animals within are exposed. Light intensity may differ as much as 80-fold in transparent cages from the top to the bottom of a rack, and differences up to 20-fold have been recorded within a cage (Schlingmann et al. 1993a,b). Management practices, such as rotating cage position relative to the light source (Greenman et al. 1982) or providing animals with ways to control their own light exposure by behavioral means (e.g., nesting or bedding material adequate for tunneling), can reduce inappropriate light stimulation. Variable-intensity lights are often used to accommodate the needs of research protocols, certain animal species, and energy conservation. However, such a system should also provide for the observation and care of the animals. Caution should be exercised as increases in daytime room illumination for maintenance purposes have been shown to change photoreceptor physiology and can alter circadian regulation (NRC 1996; Reme et al. 1991; Terman et al. 1991).

Noise and Vibration

Noise produced by animals and animal care activities is inherent in the

physical, physiologic, and behavioral needs. Environments that fail to meet the animals' needs may result in abnormal brain development, physiologic dysfunction, and behavioral disorders (Garner 2005; van Praag et al. 2000; Würbel 2001) that may compromise both animal well-being and scientific validity. The primary enclosure or space may need to be enriched to prevent such effects (see also section on Environmental Enrichment).

An appropriate housing space or enclosure should also account for the animals' social needs. Social animals should be housed in stable pairs or groups of compatible individuals unless they must be housed alone for experimental reasons or because of social incompatibility (see also section on Behavioral and Social Management). Structural adjustments are frequently required for social housing (e.g., perches, visual barriers, refuges), and important resources (e.g., food, water, and shelter) should be provided in such a way that they cannot be monopolized by dominant animals (see also section on Environmental Enrichment).

The primary enclosure should provide a secure environment that does not permit animal escape and should be made of durable, nontoxic materials that resist corrosion, withstand the rigors of cleaning and regular handling, and are not detrimental to the health and research use of the animals. The enclosure should be designed and manufactured to prevent accidental entrapment of animals or their appendages and should be free of sharp edges or projections that could cause injury to the animals or personnel. It should have smooth, impervious surfaces with minimal ledges, angles, corners, and overlapping surfaces so that accumulation of dirt, debris, and moisture is minimized and cleaning and disinfecting are not impaired. All enclosures should be kept in good repair to prevent escape of or injury to animals, promote physical comfort, and facilitate sanitation and servicing. Rusting or oxidized equipment, which threatens the health or safety of animals, needs to be repaired or replaced. Less durable materials, such as wood, may be appropriate in select situations, such as outdoor corrals, perches, climbing structures, resting areas, and perimeter fences for primary enclosures. Wooden items may need to be replaced periodically because of damage or difficulties with sanitation. Painting or sealing wood surfaces with nontoxic materials may improve durability in many instances.

Flooring should be solid, perforated, or slatted with a slip-resistant surface. In the case of perforated or slatted floors, the holes and slats should have smooth edges. Their size and spacing need to be commensurate with the size of the housed animal to minimize injury and the development of foot lesions. If wire-mesh flooring is used, a solid resting area may be beneficial, as this floor type can induce foot lesions in rodents and rabbits (Drescher 1993; Fullerton and Gilliatt 1967; Rommers and Meijerhof 1996). The size and weight of the animal as well as the duration of housing on wire-mesh floors may also play a role in the development of this condi-

exercise, manipulative activities, and cognitive challenges according to species-specific characteristics (NRC 1998a; Young 2003). Examples of enrichment include structural additions such as perches and visual barriers for nonhuman primates (Novak et al. 2007); elevated shelves for cats (Overall and Dyer 2005; van den Bos and de Cock Buning 1994) and rabbits (Stauffacher 1992); and shelters for guinea pigs (Baumans 2005), as well as manipulable resources such as novel objects and foraging devices for nonhuman primates; manipulable toys for nonhuman primates, dogs, cats, and swine; wooden chew sticks for some rodent species; and nesting material for mice (Gaskill et al. 2009; Hess et al. 2008; Hubrecht 1993; Lutz and Novak 2005; Olsson and Dahlborn 2002). Novelty of enrichment through rotation or replacement of items should be a consideration; however, changing animals' environment too frequently may be stressful.

Well-conceived enrichment provides animals with choices and a degree of control over their environment, which allows them to better cope with environmental stressors (Newberry 1995). For example, visual barriers allow nonhuman primates to avoid social conflict; elevated shelves for rabbits and shelters for rodents allow them to retreat in case of disturbances (Baumans 1997; Chmiel and Noonan 1996; Stauffacher 1992); and nesting material and deep bedding allow mice to control their temperature and avoid cold stress during resting and sleeping (Gaskill et al. 2009; Gordon 1993, 2004).

Not every item added to the animals' environment benefits their well-being. For example, marbles are used as a stressor in mouse anxiety studies (De Boer and Koolhaas 2003), indicating that some items may be detrimental to well-being. For nonhuman primates, novel objects can increase the risk of disease transmission (Bayne et al. 1993); foraging devices can lead to increased body weight (Brent 1995); shavings can lead to allergies and skin rashes in some individuals; and some objects can result in injury from foreign material in the intestine (Hahn et al. 2000). In some strains of mice, cage dividers and shelters have induced overt aggression in groups of males, resulting in social stress and injury (e.g., Bergmann et al. 1994; Haemisch et al. 1994). Social stress was most likely to occur when resources were monopolized by dominant animals (Bergmann et al. 1994).

Enrichment programs should be reviewed by the IACUC, researchers, and veterinarian on a regular basis to ensure that they are beneficial to animal well-being and consistent with the goals of animal use. They should be updated as needed to ensure that they reflect current knowledge. Personnel responsible for animal care and husbandry should receive training in the behavioral biology of the species they work with to appropriately monitor the effects of enrichment as well as identify the development of adverse or abnormal behaviors.

Like other environmental factors (such as space, light, noise, temperature, and animal care procedures), enrichment affects animal phenotype and may affect the experimental outcome. It should therefore be considered an independent variable and appropriately controlled.

Some scientists have raised concerns that environmental enrichment mc0-3(a-3(n)sa)-3,rii ii3-39 (i)12(i3-39T u(i)12(i3-33.i)-3(a)-3.i)-3-3e ietiana3(a)-3.3-M changes when animals are first introduced to outdoor housing; training of animals to cooperate with veterinary and investigative personnel (e.g., to enter chutes or cages for restraint or transport); and adequate security via a perimeter fence or other means.

Naturalistic Environments

Areas such as pastures and islands may provide a suitable environment

TABLE 3.2 Recommended Minimum Space for Commonly Used Laboratory Rodents Housed in Groups*

Animals	Weight, g	Floor Area/Animal,[a] in.^{2} (cm^2)	Height,[b] in. (cm)	Comments
Mice in groups[c]	<10 Up to 15 Up to 25 >25	6 (38.7) 8 (51.6) 12 (77.4) ≥15 (≥96.7)	5 (12.7) 5 (12.7) 5 (12.7) 5 (12.7)	Larger animals may require more space to meet the performance standards.
Female + litter		51 (330) (recommended space for the housing group)	5 (12.7)	Other breeding con gurations may require more space and will depend on considerations such as number of adults and litters, and size and age of litters.[d]
Rats in groups[c]	<100 Up to 200 Up to 300 Up to 400 Up to 500 >500	17 (109.6) 23 (148.35) 29 (187.05) 40 (258.0) 60 (387.0) ≥70 (≥451.5)	7 (17.8) 7 (17.8) 7 (17.8) 7 (17.8) 7 (17.8) 7 (17.8)	Larger animals may require more space to meet the performance standards.
Female + litter		124 (800) (recommended space for the housing group)	7 (17.8)	Other breeding con gurations may require more space and will depend on considerations such as number of adults and litters, and size and age of litters.[d]
Hamsters[c]	<60 Up to 80 Up to 100 >100	10 (64.5) 13 (83.8) 16 (103.2) ≥19 (≥122.5)	6 (15.2) 6 (15.2) 6 (15.2) 6 (15.2)	Larger animals may require more space to meet the performance standards.
Guinea pigs[c]	Up to 350 >350	60 (387.0) ≥101 (≥651.5)	7 (17.8) 7 (17.8)	Larger animals may require more space to meet the performance standards.

*The interpretation of this table should take into consideration the performance indices described in the text beginning on page 55.

[a]Singly housed animals and s-3(i)-3(m)-3(a)-3(ll)-3(po-3(c)-3(r)-3(o)-3(u h16ab <</MCID3(u h16abhnre8(t

animal may be required, while larger groups may be housed at slightly higher densities.

Studies have recently evaluated space needs and the effects of social housing, group size, and density (Andrade and Guimaraes 2003; Bartolomucci et al. 2002, 2003; Georgsson et al. 2001; Gonder and Laber 2007; Perez et al. 1997; A.L. Smith et al. 2004), age (Arakawa 2005; Davidson et al. 2007; Yildiz et al. 2007), and housing conditions (Gordon et al. 1998; Van Loo et al. 2004) for many different species and strains of rodents, and have reported varying effects on behavior (such as aggression) and experimental outcomes (Karolewicz and Paul 2001; Laber et al. 2008; McGlone et al. 2001; Rock et al. 1997; Smith et al. 2005; Van Loo et al. 2001). However, it is dif cult to compare these studies due to the study design and experimental variables that have been measured. For example, variables that may affect the animals' response to different cage sizes and housing densities include, but are not limited to, species, strain (and social behavior of the strain), phenotype, age, gender, quality of the space (e.g., vertical access), and structures placed in the cage. These issues remain complex and should be carefully considered when housing rodents.

TABLE 3.3 Recommended Minimum Space for Rabbits, Cats, and Dogs Housed in Pairs or Groups*

Animals	Weight,[a] kg	Floor Area/ Animal,[b] ft^2 (m^2)	Height,[c] in. (cm)	Comments
Rabbits	<2	1.5 (0.14)	16 (40.5)	Larger rabbits may require
	Up to 4	3.0 (0.28)	16 (40.5)	more cage height to allow
	Up to 5.4	4.0 (0.37)	16 (40.5)	animals to sit up.
	>5.4[c]	≥5.0 (≥0.46)	16 (40.5)	
Cats	≤4	3.0 (0.28)	24 (60.8)	Vertical space with perches
	>4[d]	≥4.0 (≥0.37)	24 (60.8)	is preferred and may require additional cage height.
Dogs[e]	<15	8.0 (0.74)	—[f]	Cage height should be
	Up to 30	12.0 (1.2)	—[f]	suf cient for the animals
	>30[d]	≥24.0 (≥2.4)	—[f]	to comfortably stand erect with the 0 0 5.6 7 /C0_0 1 Tf T* <0071>Tj /T

Wolfensohn 2004). Group composition is critical and numerous species-speci c factors such as age, behavioral repertoire, sex, natural social organization, breeding requirements, and health status should be taken into consideration when forming a group. In addition, due to conformational differences of animals within groups, more space or height may be required to meet the animals' physical and behavioral needs. Therefore, determination of the appropriate cage size is not based on body weight alone, and professional judgment is paramount in making such determinations (Kaufman et al. 2004; Williams et al. 2000).

TABLE 3.4 Recommended Minimum Space for Avian Species Housed in Pairs or Groups*

Animals	Weight,[a] kg	Floor area/animal,[b] ft^2 (m^2)	Height
Pigeons	—	0.8 (0.07)	Cage height should be sufficient for the animals to comfortably stand erect with their feet on the floor.
Quail	—	0.25 (0.023)	
Chickens	<0.25	0.25 (0.023)	
	Up to 0.5	0.50 (0.046)	
	Up to 1.5	1.00 (0.093)	
	Up to 3.0	2.00 (0.186)	
	>3.0[c]	$\geq$3.00 ($\geq$0.279)	

*The interpretation of this table should take into consideration the performance indices described in the text beginning on page 55.

[a]To convert kilograms to pounds, multiply by 2.2.
[b]Singly housed birds may require more space per animal than recommended for pair- or group-housed birds.
[c]Larger animals may require more space to meet performance standards (see text).

If it is necessary to house animals singly—for example, when justified for experimental purposes, for provision of veterinary care, or for incompatible animals—this arrangement should be for the shortest duration possible. If single animals are housed in small enclosures, an opportunity for periodic release into larger enclosures with additional enrichment items should be considered, particularly for animals housed singly for extended periods of time. Singly housed animals may require more space per animal than recommended for pair- or group-housed animals, while larger groups may be housed at slightly higher densities. Because of the many physical and behavioral characteristics of nonhuman primate species and the many factors to consider when using these animals in a biomedical research setting, species-specific plans for housing and management should be developed. Such plans should include strategies for environmental and psychological enrichment.

Agricultural Animals Table 3.6 lists recommended minimum space for agricultural animals commonly used in a laboratory setting. As social animals, they should be housed in compatible pairs or larger groups of compatible animals. When animals exceed the weights in the table, more space is required. For larger animals (particularly swine) it is important that the configuration of the space allow the animals to turn around and move freely (Becker et al. 1989; Bracke et al. 2002). Food troughs and water devices should be provided in sufficient numbers to allow ready access for all animals. Singly housed animals may require more space than recommended in

TABLE 3.6 Recommended Minimum Space for Agricultural Animals*

Animals/Enclosure	Weight,[a] kg	Floor Area/Animal,[b] ft^2 (m^2)
Sheep and Goats		
1	<25	10.0 (0.9)
	Up to 50	15.0 (1.35)
	>50[c]	q20.0 (q1.8)
2-5	<25	8.5 (0.76)
	Up to 50	12.5 (1.12)
	>50[c]	q17.0 (q1.53)
>5	<25	7.5 (0.67)
	Up to 50	11.3 (1.02)
	>50[c]	q15.0 (q1.35)
Swine		
1	<15	8.0 (0.72)
	Up to 25	12.0 (1.08)
	Up to 50	15.0 (1.35)
	Up to 100	24.0 (2.16)
	Up to 200	48.0 (4.32)
	>200[c]	q60.0 (q5.4)
2-5	<25	6.0 (0.54)
	Up to 50	10.0 (0.9)
	Up to 100	20.0 (1.8)
	Up to 200	40.0 (3.6)
	>200	

>5	<75	18.0 (1.62)
	Up to 200	36.0 (3.24)
	Up to 350	54.0 (4.86)
	Up to 500	72.0 (6.48)
	Up to 650	93.0 (8.37)
	>650[c]	≥108.0 (≥9.72)
Horses	—	144.0 (12.96)
Ponies		
1-4	—	72.0 (6.48)
>4/Pen	≤200	60.0 (5.4)
	>200[c]	≥72.0 (≥6.48)

*The interpretation of this table should take into consideration the performance indices described in the text beginning on page 55.

[a]To convert kilograms to pounds, multiply by 2.2.
[b]Floor area con guration should be such that animals can turn around and move freely without touching food or water troughs, have ready access to food and water, and have suf cient space to comfortably rest away from areas soiled by urine and feces (see text).
[c]Larger animals may require more space to meet performance standards including suf cient space to turn around and move freely (see text).

the table to enable them to turn around and move freely without touching food or water troughs, have ready access to food and water, and have suf- cient space to comfortably rest away from areas soiled by urine and feces.

Terrestrial Management

Behavioral and Social Management

Activity Animal Activity typically implies motor activity but also includes cognitive activity and social interaction. Animals' natural behavior and activity pro le should be considered during evaluation of suitable housing or behavioral assessment.

Animals maintained in a laboratory environment are generally restricted in their activities compared to free-ranging animals. Forced activity for reasons other than attempts to meet therapeutic or approved protocol objectives should be avoided. High levels of repetitive, unvarying behav- ior (stereotypies, compulsive behaviors) may re ect disruptions of normal behavioral control mechanisms due to housing conditions or management practices (Garner 2005; NRC 1998a).

Dogs, cats, rabbits, and man_]TJ T* [(o)-3(b)871.8 -1.2 Td Mv4amTd Mv4 additional opportunities for activity by being walked on a leash, having access to a run, or being moved into areas for social contact, play, or exploration (Wolff and Rupert 1991). Loa ng areas, exercise lots, and pastures are suitable for large farm animals, such as sheep, horses, and cattle.

Social Environment Appropriate social interactions among members of the

Institutions should urge feed vendors to periodically provide data from laboratory-based feed analyses for critical nutrients. The user should know the date of manufacture and other factors that affect the food's shelf life. Stale food or food transported and stored inappropriately can become deficient in nutrients. Upon receipt, bags of feed should be examined to ensure that they are intact and unstained to help ensure that their contents have not been potentially exposed to vermin, penetrated by liquids, or contaminated. Careful attention should be paid to quantities received in each shipment, and stock should be rotated so that the oldest food is used first.

Areas in which diets and diet ingredients are processed or stored should be kept clean and enclosed to prevent the entry of pests. Food stocks should be stored off the floor on pallets, racks, or carts in a manner that facilitates sanitation. Opened bags of food should be stored in vermin-proof containers to minimize contamination and to avoid the potential spread of pathogens. Exposure to elevated storage room temperatures, extremes in relative humidity, unsanitary conditions, and insects and other vermin hastens food deterioration. Storage of natural-ingredient diets at less than 21°C (70°F) and below 50% relative humidity is recommended. Precautions should be taken if perishable items—such as meats, fruits, and vegetables and some specialty diets (e.g., select medicated or high-fat diets)—are fed, because storage conditions may lead to variation in food quality.

Most natural-ingredient, dry laboratory animal diets stored properly can be used up to 6 months after manufacture. Nonstabilized vitamin C in manufactured feeds generally has a shelf life of only 3 months, but commonly used stabilized forms can extend the shelf life of feed. Refrigeration preserves nutritional quality and lengthens shelf life, but food storage time ensure access to food for all animals, especially if feed is restricted as part of the protocol or management routine. Food storage containers should not be transferred between areas that pose different risks of contamination without appropriate treatment, and they should be cleaned and sanitized regularly.

Management of caloric intake is an accepted practice for long-term housing of some species, such as some rodents, rabbits, and nonhuman primates, and as an adjunct to some clinical, experimental, and surgical procedures (for more discussion of food and uid regulation as an experi

et al. 2008), while cotton nestlets may lead to conjunctivitis (Bazille et al. 2001). Bedding can also in uence mucosal immunity (Sanford et al. 2002) and endocytosis (Buddaraju and Van Dyke 2003).

Softwood beddings have been used, but the use of untreated softwood shavings and chips is contraindicated for some protocols because they can affect metabolism (Vesell 1967; Vesell et al. 1973, 1976). Cedar shavings are not recommended because they emit aromatic hydrocarbons that induce hepatic microsomal enzymes and cytotoxicity (Torronen et al. 1989; Weichbrod et al. 1986, 1988) and have been reported to increase the incidence of cancer (Jacobs and Dieter 1978; Vlahakis 1977). Prior treatment with high heat (kiln drying or autoclaving) may, depending on the material and the concentration of aromatic hydrocarbon constituents, reduce the concentration of volatile organic compounds, but the amounts remaining may be suf cient to affect speci c protocols (Cunliffe-Beamer et al. 1981; Nevalainen and Vartiainen 1996).

The purchase of bedding products should take into consideration iffeff3(s)nMk7(t
ci-3(fn-3( )-235a)-3(r)-235a166(t)-3(h)-3(h)-3(o)-3(o)-3(n)-3( )-onsidh((t)-)-3(n)-3(t)

create the need for sanitation; and the rate of soiling of the surfaces of the enclosure. Some housing systems or experimental protocols may require speci c husbandry techniques, such as aseptic handling or modi cation in the frequency of bedding change.

Agents designed to mask animal odors should not be used in animal housing facilities. They cannot substitute for good sanitation practices or for the provision of adequate ventilation, and they expose animals to volatile compounds that might alter basic physiologic and metabolic processes.

Bedding/Substrate Change Soiled bedding should be removed and replaced with fresh materials as often as necessary to keep the animals clean and dry and to keep pollutants, such as ammonia, at a concentration below levels irritating to mucous membranes. The frequency of bedding change depends on multiple factors, such as species, number, and size of the animals in the primary enclosure; type and size of the enclosure; macro- and microenvironmental temperature, relative humidity, and direct ventilation of the enclosure; urinary and fecal output and the appearance and wetness of bedding; and experimental conditions, such as those of surgery or debilitation, that might limit an animal's movement or access to clean bedding. There is no absolute minimal frequency of bedding changes; the choice is a matter of professional judgment and consultation between the investigator and animal care personnel. It typically varies from daily to weekly. In some instances frequent bedding changes are contraindicated; examples include portions of the pre- or postpartum period, research objectives that will be affected, and species in which scent marking is critical and successful reproduction is pheromone dependent.

Cleaning and Disinfection of the Microenvironment The frequency of sanitation of cages, cage racks, and associated equipment (e.g., feeders and watering devices) is governed to some extent by the types of caging and husbandry practices used, including the use of regularly changed contact or noncontact bedding, regular ushing of suspended catch pans, and the use of wire-bottom or perforated-bottom cages. In general, enclosures and accessories, such as tops, should be sanitized at least once every 2 weeks.

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appropriate, chemical agents to destroy microorganisms. Cleaning with ultrasound may be a useful method for small pieces of equipment.

If automated watering systems are used, some mechanism to ensure that microorganisms and debris do not build up in the watering devices is recommended (Meier et al. 2008); the mechanism can be periodic flushing with large volumes of water or appropriate chemical agents followed by a thorough rinsing. Constant recirculation loops that use properly maintained filters, ultraviolet lights, or other devices to disinfect recirculated water are also effective. Attention should be given to the routine sanitation of automatic water delivery valves (i.e., lixits) during primary enclosure cleaning.

Conventional methods of cleaning and disinfection are adequate for most animal care equipment. However, it may be necessary to also sterilize caging and associated equipment to ensure that pathogenic or opportunistic microorganisms are not introduced into specific-pathogen-free or immunosole means of assessing the effectiveness of the sanitation program. A decision to alter the frequency of cage bedding changes or cage washing should be based on such factors as ammonia concentration, bedding condition, appearance of the cage and animals, and the number and size of animals housed in the cage.

Mechanical washer function should be evaluated regularly and include examination of mechanical components such as spray arms and moving headers as well as spray nozzles to ensure that they are functioning appropriately. If sanitation is temperature dependent, the use of temperature-sensing devices (e.g., thermometers, probes, or temperature-sensitive indicator strips) is recommended to ensure that the equipment being sanitized is exposed to the desired conditions.

Whether the sanitation process is automated or manual, regular evaluation of sanitation effectiveness is recommended. This can be performed by evaluating processed materials by microbiologic culture or the use of organic material detection systems (e.g., adenosine triphosphate [ATP] bioluminescence) and/or by con rming the removal of arti cial soil applied to equipment surfaces before washing.

Waste Disposal Conventional, biologic, and hazardous waste should be removed and disposed of regularly and safely (Hill 1999). There are several options for effective waste disposal. Contracts with licensed commercial waste disposal rms usually provide some assurance of regulatory compliance and safety. On-site incineration should comply with all federal, state, and local regulations (Nadelkov 1996).

Adequate numbers of properly labeled waste receptacles should be strategically placed throughout the facility. Waste containers should be leakproof and equipped with tight- tting lids. It is good practice to use disposable liners and to wash containers and implements regularly. There should be a dedicated waste storage area that can be kept free of insects and other vermin. If cold storage is used to hold material before disposal, a properly labeled, dedicated refrigerator, freezer, or cold room should be used that is readily sanitized.

Hazardous wastes must be rendered safe by sterilization, containment, or other appropriate means before their removal from the facility (DHHS 2009 or most recent edition; NRC 1989, 1995b). Radioactive wastes should be kept in properly labeled containers and their disposal closely coordinated with radiation safety specialists in accord with federal and state regulations; the federal government and most states and municipalities have regulations controlling disposal of hazardous wastes. Compliance with regulations concerning hazardous-agent use (see Chapter 2) and disposal is an institutional responsibility.

Infectious animal carcasses can be incinerated on site or collected by a licensed contractor. Use of chemical digesters (alkaline hydrolysis treatment) may be considered in some situations (Kaye et al. 1998; Murphy et al. 2009). Procedures for on-site packaging, labeling, transportation, and storage of these wastes should be integrated into occupational health and safety policies (Richmond et al. 2003).

Hazardous wastes that are toxic, carcinogenic, flammable, corrosive, reactive, or otherwise unstable should be placed in properly labeled containers and disposed of as recommended by occupational health and safety specialists. In some circumstances, these wastes can be consolidated or blended. Sharps and glass should be disposed of in a manner that will prevent injury to waste handlers.

Pest Control Programs designed to prevent, control, or eliminate the presence of or infestation by pests are essential in an animal environment. A regularly scheduled and documented program of control and monitoring should be implemented. The ideal program prevents the entry of vermin and eliminates their harborage in the facility (Anadon et al. 2009; Easterbrook et al. 2008). For animals in outdoor facilities, consideration should be given to eliminating or minimizing the potential risk associated with pests and predators.

Pesticides can induce toxic effects on research animals and interfere with experimental procedures (Gunasekara et al. 2008). They should be used in animal areas only when necessary and investigators whose animals may be exposed to them should be consulted beforehand. Use of pesticides should be recorded and coordinated with the animal care management staff and be in compliance with federal, state, or local regulations. Whenever possible, nontoxic means of pest control, such as insect growth regulators (Donahue et al. 1989; Garg and Donahue 1989; King and Bennett 1989; Verma 2002) and nontoxic substances (e.g., amorphous silica gel), should be used. If traps are used, methods should be humane; traps that catch pests alive require frequent observation and humane euthanasia after capture (Mason and Littin 2003; Meerburg et al. 2008).

Emergency, Weekend, and Holiday Care Animals should be cared for by qualified personnel every day, including weekends and holidays, both to safeguard their well-being and to satisfy research requirements. Emergency veterinary care must be available after work hours, on weekends, and on holidays.

In the event of an emergency, institutional security personnel and fire or police officials should be able to reach people responsible for the animals. Notification can be enhanced by prominently posting emergency procedures, names, or telephone numbers in animal facilities or by placing them in the security department or telephone center. Emergency procedures for handling special facilities or operations should be prominently posted and personnel trained in emergency procedures for these areas. A disaster plan that takes into account both personnel and animals should be prepared as part of the overall safety plan for the animal facility. The colony manager or veterinarian responsible for the animals should be a member of the appropriate safety committee at the institution, an “official responder” in the institution, and a participant in the response to a disaster (Vogelweid 1998).

Population Management

Identification Animal records are useful and variable, ranging from limited information on identification cards to detailed computerized records for individual animals (Field et al. 2007). Means of animal identification include room, rack, pen, stall, and cage cards with written, bar-coded, or radio frequency identification (RFID) information. Identification cards should include the source of the animal, the strain or stock, names and contact information for the responsible investigator(s), pertinent dates (e.g., arrival date, birth date, etc.), and protocol number when applicable. Genotype information, when applicable, should also be included, and consistent, unambiguous abbreviations should be used when the full genotype nomenclature (see below) is too lengthy.

In addition, the animals may wear collars, bands, plates, or tabs or be marked by colored stains, ear notches/punches and tags, tattoos, subcutaneous transponders, and freeze brands. As a method of identification of small rodents, toe-clipping should be used only when no other individual identification method is feasible. It may be the preferred method for neonatal mice up to 7 days of age as it appears to have few adverse effects on behavior and well-being at this age (Castelhano-Carlos et al. 2010; Schaefer et al. 2010), especially if toe clipping and genotyping can be combined. Under all circumstances aseptic practices should be followed. Use of anesthesia or analgesia should be commensurate with the age of the animals (Hankenson et al. 2008).

Recordkeeping Records containing basic descriptive information are essential for management of colonies of large long-lived animals and should be maintained for each animal (Dyke 1993; Field et al. 2007; NRC 1979a). These records often include species, animal identifier, sire and/or dam identifier, sex, birth or acquisition date, source, exit date, and final disposition. Such animal records are essential for genetic management and historical assessments of colonies. Records of rearing and housing histories, mating histories, and behavioral profiles are useful for the management of many species, especially nonhuman primates (NRC 1979a). Relevant recorded information should be provided when animals are transferred between institutions.

Medical records for individual animals can also be valuable, especially for dogs, cats, nonhuman primates, and agricultural animals (Suckow and Doerning 2007). They should include pertinent clinical and diagnostic information, date of inoculations, history of surgical procedures and postoperative care, information on experimental use, and necropsy findings where applicable.

Basic demographic information and clinical histories enhance the value of individual animals for both breeding and research and should be readily accessible to investigators, veterinary staff, and animal care staff.

Breeding, Genetics, and Nomenclature Genetic characteristics are important with regard to the selection and management of animals for use in breeding colonies and in biomedical research (see Appendix A). Pedigree information allows appropriate selection of breeding pairs and of experi-

temperature. The physical environment of the secondary enclosure, such as a room, constitutes the macroenvironment.

Water Quality

The composition of the water (water quality) is essential to aquatic animal well-being, although other factors that affect terrestrial microenvironments are also relevant. Water quality parameters and life support systems for aquatic animals will vary with the species, life stage, the total biomass supported, and the animals' intended use (Blaustein et al. 1999; Fisher 2000; Gresens 2004; Overstreet et al. 2000; Schultz and Dawson 2003). The success and adequacy of the system depend on its ability to match the laboratory habitat to the natural history of the species (Godfrey and Sanders 2004; Green 2002; Lawrence 2007; Spence et al. 2008).

Characteristics of the water that may affect its appropriateness include temperature, pH, alkalinity, nitrogen waste products (ammonia, nitrite, and nitrate), phosphorus, chlorine/bromine, oxidation-reduction potential, conductivity/salinity, hardness (osmolality/dissolved minerals), dissolved oxygen, total gas pressure, ion and metal content, and the established microbial ecology of the tank. Water quality parameters can directly affect animal well-being; different classes, species, and ages in a species may have different water quality needs and sensitivities to changes in water quality parameters.

Routine meT(e)-36-3(u)-3(r)-e(a)-3(m)-3(e)-(e)-3(c)-3(t)--4( )-226(a)-4(n)-32(t)-26
p1.2 Td [(t)-8(e)-8(s)-3( )-104ne s, (q)-74sti(q)-7(s)-3(s)-3( )-40()-3(t)-3(i)-3(a)-3(l)-

or neutralized before use in aquatic systems (Tompkins and Tsai 1976; Wedemeyer 2000).

Life Support System

The phraselife support systemrefers to the physical structure used to contain the water and the animals as well as the ancillary equipment used to move and/or treat the water. Life support systems may be simple (e.g., a container to hold the animal and water) or extremely complex (e.g., a fully automated recirculating system). The type of life support system used depends on several factors including the natural habitat of the species, age/size of the species, number of animals maintained, availability and characteristics of the water required, and the type of research.

Life support systems typically fall into three general categories: recirculating systems where water (all or part) is moved around a system, ow-through systems where water is constantly replaced, or static systems where water is stationary and periodically replenished or replaced. The water may be fresh, brackish, or salt and is maintained at speci c temperatures depending on the species' needs.

The source of water for these systems typically falls into four general categories: treated wastewater (e.g., municipal tap water), surface water (e.g., rivers, lakes, or oceans), protected water (e.g., well or aquifer water), or arti cial water (e.g., reverse osmosis or distilled water). Arti cial saltwater may be created by adding appropriate salt to freshwater sources. Source water selection should be based on the provision of a consistent or constant supply, incoming biosecurity level requirements, water volumes needed, species selection, and research considerations.

Recirculating systems are common in indoor research settings where high-density housing systems are often needed. Most recirculating systems are designed to exchange a speci c volume of water per unit time and periodically introduce fresh water into the system. These systems are the most mechanically advanced, containing biologic lters (bio lters) that promote conversion of ammonia to nitrite and nitrate via nitrifying bacteria, protein skimmers (foam fractionators) and particulate lters to remove undissolved and dissolved proteins and particulate matter, carbon lters to remove dissolved chemicals, and ultraviolet or ozone units to disinfect the water. The systems generally contain components to aerate and degas the water (to prevent gas oversaturation) and to heat or cool it, as well as automated dosing systems to maintain appropriate pH and conductivity. Not all elements are present in all systems and some components may accomplish multiple functions. Recirculating systems may be designed so that multiple individual tanks are supplied with treated water from a single source, as is the case with "rack" systems used for zebra sh (Danio rerio) and Xenopus

pensate for these thermal and moisture loads. Macroenvironmental relative humidity levels are generally de ned by safety issues and staff comfort, these may cause subclinical effects (Smith et al. 2007). Vibration through floors can be reduced by using isolation pads under aquaria racks. Some facilities elect to place major components of the life support system (e.g., filters, pumps, and biofilters) outside the animal rooms to reduce vibration and noise.

Aquatic Housing

Microenvironment (Primary Enclosure)

The primary enclosure (a tank, raceway, pond, or pen holding water and the animal) defines the limits of an animal's immediate environment. In research settings, acceptable primary enclosures

- allow for the normal physiological and behavioral needs of the animals, including excretory function, control and maintenance of body temperature, normal movement and postural adjustments, and, where indicated, reproduction. In some poikilothermic reptiles and amphibians, microenvironmental temperature gradients may be needed for certain physiologic functions such as feeding and digestion.
- allow conspecific social interactions (e.g., schooling in fish species).
- provide a balanced, stable environment that supports the animal's physiologic needs.
- provide the appropriate water quality and characteristics, and permit monitoring, filling, refilling, and changing of water.
- allow access to adequate food and removal of food waste.
- restrict escape or accidental entrapment of animals or their appendages.
- are free of sharp edges and/or projections that could cause injury.

housing for many species. When used, enrichment should elicit species-appropriate behaviors and be evaluated for safety and utility.

Generally, schooling fish species are housed with conspecifics, and many amphibians, especially anuran species, may be group housed. Aggression in aquatic animals does occur (van de Nieuwegiessen et al. 2008; Speedie and Gerlai 2008) and, as for terrestrial animals, appropriate monitoring and intervention may be necessary (Matthews et al. 2002; Torreilles and Green 2007). Some species need appropriate substrate (e.g., gravel) to reproduce or need substrate variety to express basic behaviors and maintain health (Overstreet et al. 2000). Improved breeding success in enriched environments has been reported but further research in this area is needed (Carfagnini et al. 2009). For many species (including, e.g., *X. laevis*), visual barriers, hides, and shading are appropriate (Alworth and Vasquez 2009; Torreilles and Green 2007). Most semiaquatic reptiles spend some time on land (basking, feeding, digesting, and ovipositing) and terrestrial areas should be provided as appropriate.

Sheltered, Outdoor, and Naturalistic Housing

Animals used in aquaculture are often housed in situations that mimic agricultural rearing and may be in outdoor and/or sheltered raceways, ponds, or pens with high population densities. In these settings, where natural predation and mortalities occur, it may be appropriate to measure animal “numbers” by using standard aquaculture techniques such as final production biomass (Borski and Hodson 2003).

Space

Space recommendations and housing density vary extensively with the species, age/size of the animals, life support system, and type of research (Browne et al. 2003; Green 2009; Gresens 2004; Hilken et al. 1995; Matthews et al. 2002). In the United States, for example, adult zebrafish (*Danio rerio*) in typical biomedical research settings are generally housed 5 adult fish per liter of water (Matthews et al. 2002), but this housing density varies when breeding and for housing younger animals (Matthews et al. 2002). This guidance is not necessarily relevant for other species of fish, and may change as research advances (Lawrence 2007). *X. laevis* adults may be housed at 2 liters of water per frog (NRC 1974), but a wide variety of housing systems are currently used in research settings (Green 2009). Institutions, investigators, and IACUC members should evaluate the appropriate needs of each species during program evaluations and facility inspections and continue to review ongoing research in these areas.

Aquatic Management

Behavior and Social Management

Visual evaluations of aquatic and semiaquatic animals are typically used for monitoring. To avoid damage to the protective mucus layers of the skin and negative effects on immune function (De Veer et al. 2007; Subramanian et al. 2007; Tsutsui et al. 2005), handling of these species should be kept to the minimum required (Bly et al. 1997). Appropriate handling techniques vary widely depending on the species, age/size, holding system, and specific research need (Fisher 2000; Matthews et al. 2002; Overstreet et al. 2000); they should be identified at the facility or individual protocol level.

Latex gloves have been associated with toxicity in some amphibians (Gutleb et al. 2001). The use of appropriate nets by well-trained personnel can reduce skin damage and thus stress. Nets should be cleaned and disinfected appropriately when used in different systems and should be dedicated to animals of similar health status whenever possible.

Exercise and activity levels for aquatic species are minimally described but informed decisions may be extrapolated from studies of behavior of the same or similar species in the wild (Spence et al. 2008). Some aquatic species do not rest and constantly swim; others may rest all or a significant portion of the day. Water flow rates and the provision of hides or terrestrial resting platforms (e.g., for some reptiles and amphibians) need to be appropriate for species and life stage.

Husbandry

Food The general principles relating to feeding of terrestrial animals are applicable to aquatic animals. Food should be stored in a type-appropriate manner to preserve nutritional content, minimize contamination, and prevent entry of pests. Food delivery methods should ensure that all animals are able to access food for a sufficient period of time while minimizing feeding aggression and nutrient loss. Feeding methods and frequency vary widely depending on the species, age/size of species, and type of life support system. Many aquatic or semiaquatic species are not provided with food ad libitum in the tank, and in some cases may not be fed daily.

Commercial diets (e.g., pellets, flakes) are available for certain species and storage time should be based on manufacturer recommendations or follow commonly accepted practices. In aquatic systems, particularly in fish rearing or when maintaining some amphibian and reptile species, the use of live foods (e.g., *Artemia* sp. larva, crickets, or mealworm beetle larvae) is common. Live food sources need to be maintained and managed to ensure a steady supply and the health and suitability of the organism as a food. Care should be taken to feed a complete diet to avoid nutritional de ciencies.

Water (see also section on Water Quality)Aquatic animals need access to

Disinfection is usually accomplished through water treatment (e.g., filtration and application of UV light or ozone) and/or water changes. Chlorine and most chemical disinfectants are inappropriate for aquatic systems containing animals as they are toxic at low concentrations; when used to disinfect an entire system or system components, extreme care must be taken to ensure that residual chlorine, chemical, and reactive byproducts are neutralized or removed. The type of monitoring and frequency varies depending on the disinfection method, the system, and the animals.

Algal growth is common in aquatic systems and increases with the presence of nitrogen and phosphorus, particularly in the presence of light. Excessive growth may be an indication of elevated nitrogen or phosphorus levels. Algal species seen with recirculating systems are generally nontoxic, although species capable of producing toxins exist. Algae are typically removed using mechanical methods (i.e., scrubbing or scraping). Limiting algal growth is important to allow viewing of the animals in the enclosure. Cyanobacteria (commonly called blue-green algae) growth is also possible and may be common in freshwater aquaculture. The same factors that promote algae growth also promote cyanobacteria growth. As with algae, while most species are harmless, some species can produce clinically relevant toxic compounds (Smith et al. 2008).

Tank (cage) changing and disinfection are conducted at frequencies using methods that often differ from terrestrial systems. Because waste is dissolved in the water and/or removed as solids by siphoning or filtration, regular changing of tanks is not integral to maintaining adequate hygiene in typical aquatic systems. The frequency of cleaning and disinfection should be determined by water quality, which should permit adequate viewing of the animals, and animal health monitoring. System components such as lids on fish tanks, which may accumulate feed, may require sanitation as often as weekly depending on the frequency and type of feed and the system's design.

Cleaning and Disinfection of the Macroenvironment As with terrestrial systems, all components of the animal facility, including animal rooms and support spaces (e.g., storage areas, cage-washing facilities, corridors, and procedure rooms), should be regularly cleaned and disinfected as appropriate to the circumstances and at a frequency determined by the use of the area and the nature of likely contamination. Cleaning agents should be chosen and used with care to ensure there is no secondary contamination of the aquatic systems.

Cleaning implements should be made of materials that resist corrosion and withstand regular sanitation. They should be assigned to specific areas and should not be transported between areas with different risks of contamination without prior disinfection. Worn items should be replaced regularly.

Waste Disposal Wastewater treatment and disposal may be necessary in some facilities depending on water volume, quality, and chemical constituents. Local regulations may limit or control the release of wastewater.

Pest Control Terrestrial animal pest control principles apply to aquatic systems but, due to transcutaneous absorption, aquatic and semiaquatic species may be more sensitive to commonly used pest control agents than terrestrial animals. Before use, an appropriate review of chemicals and methods of application is necessary.

Emergency, Weekend, and Holiday Care As with terrestrial species, aquatic animals should receive daily care from qualified personnel who have a sufficient understanding of the housing system to identify malfunctions and, if they are unable to address a system failure of such magnitude that it requires resolution before the next workday, access to staff who can respond to the problem. Automated monitoring systems are available and may be appropriate depending on system size and complexity. Appropriate emergency response plans should be developed to address major system failures.

Population Management

Identification Identification principles are similar to those for terrestrial animals. Identification criteria are based on the species and housing system. Identification methods available for use in aquatic species include fin clipping, genetic testing (Matthews et al. 2002; Nickum et al. 2004), identificaillnesses; animal transfers within and out of the facility; and fertilization/hatching information (Koerber and Kalishman 2009; Matthews et al. 2002). Records should be kept concerning feeding information (e.g., food offered, acceptance), nonexpired food supplies to ensure sustenance of nutritional profile, and any live cultures (e.g., hatch rates and information to ensure suppliers' recommendations are being met; Matthews et al. 2002).

Records of water quality testing for system and source water and maintenance activities of the life support system components are important for tracking and ensuring water quality. The exact water quality parameters tested and testing frequency should be clearly established and will vary with such factors as the type of life support system, animals, and research, as discussed under Water Quality. Detailed tracking of animal numbers in aquatic systems is often possible with accurate records of transfers, breeding, and mortalities (Matthews et al. 2002). In some cases where animals are housed in large groups (e.g., some *Xenopus* colonies) periodic censuses may be undertaken to obtain an exact count. In large-scale aquaculture research it may be more appropriate to measure biomass of the system versus actual numbers of animals (Borski and Hodson 2003).

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4

Veterinary Care

Veterinary care is an essential part of an animal care and use Program.

from these sources and the potential for introducing health risks to personnel and other facility animals. Breeding colonies should be established based on need and managed according to principles of animal reduction such as cryopreservation for rodent stocks or strains (Robinson et al. 2003).

Transportation of Animals

Transportation of animals is governed by a number of US regulatory agencies and international bodies. The Animal Welfare Regulations (USDA 1985) set standards for interstate and export/import transportation of regulated species; the International Air Transport Association (IATA) updates the Live Animals Regulations annually and IATA member airlines and many countries agree to comply with these regulations to ensure the safe and humane transport of animals by air (IATA 2009). The Centers for Disease Control and Prevention and USDA enforce regulations to prevent the introduction, transmission, or spread of communicable diseases and regulate the importation of any animal or animal product capable of carrying a zoonotic disease. The US Fish and Wildlife Service regulates importation/exportation of wild vertebrate and invertebrate animals and their tissues. As the national authority arm of the Convention on International Trade in Endangered Spereceipt. Shipping should be coordinated to ensure that animals arrive during normal business hours or, if delivery occurs outside of this time, that someone is available to receive them. Defining and delegating responsibility to the appropriate persons, who are knowledgeable about the needs of the species being shipped, will help ensure effective communication and planning of animal transport (AVMA 2002).

All animals in transit within and between institutions or jurisdictions should be accompanied by appropriate documentation to minimize delays in shipping and receipt. Documentation may include health certificates, sending and receiving institutions' addresses and contacts, emergency procedures and veterinary contact information, and agency permits as needed.

For noncommercial sources of animals, in particular, it is important for the veterinarian or the veterinarian's designee to review the health status and other housing and husbandry requirements before authorizing shipment of animals. This action will ensure that effective quarantine practices are implemented for incoming animals and address any special requirements needed to ensure animal well-being (Otto and Tolwani 2002). Special considerations may be necessary for transporting animals during certain phases of their life or in certain conditions, such as pregnant, perinatal, and geriatric animals; animals with preexisting medical conditions (e.g., diabetes mellitus); and animals surgically prepared by the supplier (FASS 2010).

Although ensuring animal biosecurity during transportation is always important, it is of particular importance for immunocompromised, genetically modified, and specific pathogen-free rodents (Jacoby and Lindsey 1998). For these animals, reinforced disposable shipping containers with filter-protected ventilation openings and internal food and water sources help ensure that microbial contamination does not occur during transit. Commercial vendors are experienced in animal transport and typically use dedicated transport systems and protocols to minimize microbiologic contamination. Noncommercial or interinstitutional transfer of rodents poses a higher risk of microbial contamination since the individuals involved may lack the required knowledge and animal biosecurity capabilities to maintain the animals' health status. Risks due to in-transit microbial contamination of shipping container surfaces can be reduced by decontaminating the surfaces before placement of the containers in clean sites of animal facilities (NRC 1996, 2006). Transportation of animals in private vehicles is discouraged because of potential animal biosecurity, safety, health, and liability risks for the animals, personnel, and institution.

For aquatic species and amphibians, special considerations are required for transportation in an aqueous or sufficiently moist environment, and special attention should be given to avoiding temperature extremes for poikilotherms.

In all cases, appropriate loading and unloading facilities should be provided for the safe and secure transfer of animals at an institution. Facilities and procedures should be in place to help ensure that the environment at the site does not pose risks to animal well-being or personnel safety. During times of extreme temperatures animal transport may be detrimental to animal well-being and therefore may not be possible unless an appropriately heated or cooled means of transportation is available (Robertshaw 2004; Schrama et al. 1996).

PREVENTIVE MEDICINE

Disease prevention is an essential component of comprehensive veterinary medical care and biosecurity programs. Effective preventive medicine enhances the research value of animals by maintaining healthy animals and minimizing nonprotocol sources of variation associated with disease and inapparent infection, thus minimizing animal waste and potential effects on well-being. Preventive medicine programs consist of various combinations of policies, procedures, and equipment related to quarantine and stabilization and the separation of animals by species, source, and health status.

Animal Biosecurity

Animal biosecurity refers to all measures taken to identify, contain, prevent, and eradicate known or unknown infections that may cause clinical disease or alter physiologic and behavioral responses or otherwise make the animals unsuitable for research. Animal biosecurity practices should be applied to all species, but they are most important when housing large numbers of animals in intensive housing conditions (e.g., laboratory rodents). Limiting exposure of animals to infectious disease agents requires consideration of physical plant layout and operational practices. Separation of clean and soiled caging and equipment, and sometimes the associated staff, is often fundamental to success.

> Animal biosecurity includes all measures to control known or unknown infections in laboratory animals.

A successful animal biosecurity program incorporates a number of elements: procedures that ensure that only animals of a desired defined health status enter the facility; personnel and materials, especially consumables, that do not serve as fomites; practices that reduce the likelihood of cross contamination if an infectious agent is inadvertently introduced; a comprehensive ongoing system for evaluating animals' health status, including access to all animals; and containment and eradication, if desired, of introduced infectious agents. Related components include procedures for evaluating and selecting appropriate animal suppliers (these may include quarantine and determination of animal health status if unknown); treatment of animals or their products at entry to minimize disease risks (e.g., surface disinfection of fish eggs); a comprehensive pest control program that may include evaluation of the health status of feral animals; procedures to ensure that all biologics administered to animals are free of contamination; and procedures for intra- and interfacility animal transport (e.g., transport of animals to laboratory and other facilities outside the animal facility can present challenges to animal biosecurity) (Balaban and Hampshire 2001). Additional details pertaining to these topics are available in the sections of Chapter 2 that deal with occupational health and safety.

Quarantine and Stabilization

Quarantine is the separation of newly received animals from those already in the facility, in a way that prevents potential spread of contaminants, until the health and possibly the microbial status of the newly received animals have been determined. Transportation can be stressful and may induce recrudescence of subclinical infections harbored by an animal.

An effective quarantine program minimizes the risk of introduction of

Depending on the health status of the colony animals and consistent with the animal biosecurity program in place, rodents or other animals being moved outside an animal facility for procedures (e.g., imaging or behavioral testing) may need to be held separately from their colony of origin until their health status is evaluated.

Regardless of whether the animals are quarantined, newly received animals should be given a period for physiologic, behavioral, and nutritional acclimation before their use (Obernier and Baldwin 2006). The length of time for acclimation will depend on the type and duration of animal transportation, the species, and the intended use of the animals. For animals not typically housed in research settings, consideration should be given to providing means to assist with their acclimation (e.g., shearing sheep before they are brought indoors). The need for an acclimation period has been demonstrated in mice, rats, guinea pigs, nonhuman primates, and goats, and time for acclimation is likely important for other species as well (Capitanio et al. 2006; Conour et al. 2006; Kagira et al. 2007; Landi et al. 1982; Prasad et al. 1978; Sanhouri et al. 1989; Tuli et al. 1995).

Separation by Health Status and Species

Physical separation of animals by species is recommended to prevent interspecies disease transmission and to eliminate the potential for anxiety and physiologic and behavioral changes due to interspecies conflict (Arndt et al. 2010). Such separation is usually accomplished by housing different species in separate rooms, but in some instances it may be possible with cubicles, laminar flow units, cages that have filtered air or separate ventilation, or isolators. It may also be acceptable to house different species in the same room—for example, two species that have a similar pathogen status and are behaviorally compatible (Pritchett-Corning et al. 2009), or aquatic species, as long as nets and other animal handling devices remain separate between systems.

In some species subclinical or latent infections can cause clinical disease if transmitted to another species. A few examples may serve as a guide in determining the need for separate housing by species:

- Helicobacter bilis can infect rats and mice and may induce clinical disease in both species (Haines et al. 1998; Jacoby and Lindsey 1998; Maggio-Price et al. 2002).
- As a rule, New World (South and Central American), Old World African, and Old World Asian species of nonhuman primates should be housed in separate rooms. Simian hemorrhagic fever (Renquist 1990) and simian immunodeficiency virus (Hirsch et al. 1991; Murphey-Corb et al. 1986), for example, cause only subclinical

infections in African species but induce clinical disease in Asian species.

- Some species should be housed in separate rooms even though they are from the same geographic region. For example, squirrel monkeys (*Saimiri sciureus*) and tamarins (*Saguinus oedipus*) may be latently infected with herpesviruses (*Herpesvirus saimiri* and *H. tamarinus*, respectively2elys and serology. If a disease or infectious agent is identified in a facility or colony, the choice of therapy should be made by the veterinarian in consultation with the investigator. If the animal is to remain in the study, the selected treatment plan should be therapeutically sound and, when possible, interfere minimally with the research process.

Subclinical microbial infections (see Appendix A, Pathology, Clinical Pathology, and Parasitology) occur frequently in conventionally maintained rodents but can also occur in facilities designed and maintained for production and use of pathogen-free rodents if the microbial barrier is breached. Examples of infectious agents that can be subclinical but that may induce immunologic changes or alter physiologic, pharmacologic, or toxicologic responses are noroviruses, parvoviruses, mouse he,y or als hp7D-3(l)0-2(s)-2( )26(a) -litio andc program‘s requirements, which will vary by institution, species used, and the nature of the animal use. To be effective in providing clinical care, the veterinarian should be familiar with the species and various uses of animals in the institutional research, teaching, testing, or production programs and have access to medical and experimental treatment records.

Medical Management

There should be a timely and accurate method for communication of any abnormalities in or concerns about animal health, behavior, and well-being to the veterinarian or the veterinarian’s designee. The responsibility for communicating these concerns rests with all those involved with animal care and use. Reports should be triaged to ensure that animals most in need receive priority attention, and the veterinarian or veterinarian’s designee should perform an objective assessment of the animal(s) to determine an appropriate course of action.

Well-planned experiments with clearly delineated scientific and humane endpoints will help to ensure that a contingency plan is in place for problems that may arise during the study (see Chapter 2, Experimental and Humane Endpoints). For animals on research protocols, the veterinarian or veterinarian’s designee should make every effort to discuss any problems with the principal investigator or project director to jointly determine the most appropriate course of treatment or action. Standard operating procedures (SOPs) may be developed for recurrent health conditions to expedite treatment. Recurrent or significant problems involving experimental animal health should be communicated to the IACUC, and all treatments and outcomes should be documented (USDA 1997).

Emergency Care

Procedures must be in place to provide for emergency veterinary care both during and outside of regularly scheduled hours. Such procedures must enable animal care and research staff to make timely reports of animal injury, illness, or death. A veterinarian or the veterinarian’s designee must be available to expeditiously assess the animal’s condition, treat the animal, investigate an unexpected death, or advise on euthanasia. In the case of a pressing health problem, if the responsible person (e.g., investigator) is not available or if the investigator and veterinary staff cannot reach consensus on treatment, the veterinarian must have the authority, delegated by senior administration (see Chapter 2, Institutional Official and Attending Veterinarian) and the IACUC, to treat the animal, remove it from the experiment, institute appropriate measures to relieve severe pain or distress, or perform euthanasia if necessary.

Recordkeeping

Medical records are a key element of the veterinary care program and are considered critical for documenting animal well-being as well as tracking animal care and use at a facility. A veterinarian should be involved in establishing, reviewing, and overseeing medical and animal use records (Field et al. 2007; Suckow and Doerning 2007). All those involved in animal care and use must comply with federal laws and regulations regarding human and veterinary drugs and treatments. Drug records and storage procedures should be reviewed during facility inspections.

SURGERY

Successful surgical outcomes require appropriate attention to presurgical planning, personnel training, anesthesia, aseptic and surgical technique, assessment of animal well-being, appropriate use of analgesics, and animal physiologic status during all phases of a protocol involving surgery and postoperative care (see Appendix A, Anesthesia, Pain, and Surgery). The individual impact of those factors will vary according to the complexity of procedures involved and the species of animal used. A team approach to a surgical project often increases the likelihood of a successful outcome by providing input from persons with different expert erg(c)-3(o)--3(o)-3(m)-3( )-1w in113
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traf c (AORN 2006; Bartley 1993). If it is necessary to use an operating room for other purposes, it is imperative that the room be returned to an appropriate level of hygiene before its use for major survival surgery.

major or minor should be evaluated on a case-by-case basis by the veterinarian and IACUC.

Emergency situations sometimes require immediate surgical attention under less than ideal conditions. For example, if an animal maintained outdoors needs surgical attention, movement to a surgical facility might be impractical or pose an unacceptable risk to the animal. Such situations often require more intensive aftercare and may pose a greater risk of postoperative

Specific sterilization methods should be selected on the basis of the physical characteristics of the materials to be sterilized (Callahan et al. 1995; Schofield 1994) and sterilization indicators should be used to validate that materials have been properly sterilized (Berg 1993). Autoclaving and plasma and gas sterilization are effective methods most commonly used to sterilize instruments and materials. Alternative methods, used primarily for rodent surgery, include liquid chemical sterilants and dry heat sterilization. Liquid chemical sterilants should be used with appropriate contact times and instruments should be rinsed with sterile water or saline before use. Bead or dry heat sterilizers are an effective and convenient means of rapidly sterilizing the working surfaces of surgical instruments but care should be taken to ensure that the instrument surfaces have cooled sufficiently before touching animal tissues to minimize the risk of burns. Alcohol is neither a sterilant nor a high-level disinfectant (Rutala 1990) but may be acceptable for some procedures if prolonged contact times are used (Huerkamp 2002).

Intraoperative Monitoring

Careful monitoring and timely attention to problems increase the likelihood of a successful surgical outcome (Kuhlman 2008). Monitoring includes routine evaluation of anesthetic depth and physiologic functions and conditions, such as body temperature, cardiac and respiratory rates and pattern (Flegal et al. 2009), and blood pressure (Kuhlman 2008), and should be appropriately documented. Use of balanced anesthesia, including the addition of an intraoperative analgesic agent, can help minimize physiologic fluctuations during surgery. Maintenance of normal body temperature minimizes cardiovascular and respiratory disturbances caused by anesthetic trained personnel. Particular attention should be given to thermoregulation, cardiovascular and respiratory function, electrolyte and uid balance, and management of postoperative pain or discomfort. Additional care may be warranted, including long-term administration of parenteral uids, analgesics, and other drugs, as well as care of surgical incisions. Appropriate medical records should also be maintained.

After recovery from anesthesia, monitoring is often less intense but should include attention to basic biologic functions of intake and elimination and to behavioral signs of postoperative pain, monitoring top65(t)-3(o)o-1 54 5to (all), anorexia (all), rapid or labored respiration (rodents, birds, sh), lack of grooming (mammals and birds), increased aggression (mammals

used in combination with appropriate analgesics and anesthetics to provide balanced anesthesia and to minimize stress associated with perioperative procedures. Neuromuscular blocking agents (e.g., pancuronium) are sometimes used to paralyze skeletal muscles during surgery in which general anesthetics have been administered (Klein 1987); because this paralysis eliminates many signs and reflexes used to assess anesthetic depth, autonomic nervous system changes (e.g., sudden changes in heart rate and blood pressure) can be indicators of pain related to an inadequate depth of anesthesia. It is imperative that any proposed use of neuromuscular blocking drugs be carefully evaluated by the veterinarian and IACUC to ensure the well-being of the animal. Acute stress is believed to be a consequence of paralysis in a conscious state and it is known that humans, if conscious, can experience distress when paralyzed with these drugs (NRC 2008; Van Sluyters and Oberdorfer 1991). If paralyzing agents are to be used, the appropriate amount of anesthetic should first be defined on the basis of results of a similar procedure using the anesthetic without a blocking agent (NRC 2003, 2008, 2009a).

EUTHANASIA

Euthanasia is the act of humanely killing animals by methods that induce rapid unconsciousness and death without pain or distress. Unless a deviation is justified for scientific or medical reasons, methods should be consistent with the *AVMA Guidelines on Euthanasia* (AVMA 2007 or later editions). In evaluating the appropriateness of methods, some of the criteria that should be considered are ability to induce loss of consciousness and death with no or only momentary pain, distress, or anxiety; reliability; irreversibility; time required to induce unconsciousness; appropriateness for the species and age of the animal; compatibility with research objectives; and the safety of and emotional effect on personnel.

Euthanasia may be planned and necessary at the end of a protocol or as a means to relieve pain or distress that cannot be alleviated by analgesics, sedatives, or other treatments. Criteria for euthanasia include protocol-specific endpoints (such as degree of a physical or behavioral deficit or tumor size) that will enable a prompt decision by the veterinarian and the investigator to ensure that the endpoint is humane and, whenever possible, the scientific objective of the protocol is achieved (see Chapter 2).

Standardized methods of euthanasia that are predictable and controllable should be developed and approved by the AV and IACUC. Euthanasia should be carried out in a manner that avoids animal distress. Automated systems for controlled and staged delivery of inhalants may offer advantages for species killed frequently or in large numbers, such as rodents (McIntyre et al. 2007). Special consideration should be given to euthanasia of fetuses and larval life forms depending on species and gestational age (Artwohl et al. 2006).

The selection of specific agents and methods for euthanasia will depend on the species involved, the animal's age, and the objectives of the protocol. Generally, chemical agents (e.g., barbiturates, nonexplosive inhalant anesthetics) are preferable to physical methods (e.g., cervical dislocation, decapitation, use of a penetrating captive bolt); however, scientific considerations may preclude the use of chemical agents for some protocols.

Although carbon dioxide (CO_2) is a commonly used method for rodent euthanasia, there is ongoing controversy about its aversive characteristics as an inhalant euthanasia agent. This is an area of active research (Conlee et al. 2005; Danneman et al. 1997; Hackbarth et al. 2000; Kirkden et al. 2008; Leach et al. 2002; Niel et al. 2008) and further study is needed to optimize the methods for CO_2 euthanasia in rodents (Hawkins et al. 2006). The acceptability of CO_2 as a euthanasia agent for small rodents should be evaluated as new data become available. Furthermore, because neonatal rodents are resistant to the hypoxia-inducing effects of CO_2 and require longer exposure times to the agent (Artwohl et al. 2006), alternative methods should be considered (e.g., injection with chemical agents, cervical dislocation, or decapitation; Klaunberg et al. 2004; Pritchett-Corning 2009).

It is essential that euthanasia be performed by personnel skilled in methods for the species in question and in a professional and compassionate manner. Special attention is required to ensure proficiency when a physical method of euthanasia is used. Death must be confirmed by personnel trained to recognize cessation of vital signs in the species being euthanized. A secondary method of euthanasia (e.g., thoracotomy or exsanguination) can be also used to ensure death. All methods of euthanasia should be reviewed and approved by the veterinarian and IACUC.

Euthanizing animals is psychologically difficult for some animal care, veterinary, and research personnel, particularly if they perform euthanasia repetitively or are emotionally attached to the animals being euthanized (Arluke 1990; NRC 2008; Rollin 1986; Wolfle 1985). When delegating euthanasia responsibilities, supervisors should be sensitive to this issue.

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Building materials for animal facilities should be selected to facilitate efficient and hygienic operation. Durable, moisture- and vermin-proof, fire-resistant, seamless materials are most desirable for interior surfaces, which should be highly resistant to the effects of cleaning agents, scrubbing, high-pressure sprays, and impact. Paints and glazes should be nontoxic if used on surfaces with which animals will have direct contact. In the construction of outdoor facilities, consideration should be given to surfaces that withstand the elements and can be easily maintained.

Location

Quality animal management and human comfort and health protection require separation of animal facilities from personnel areas, such as offices and conference rooms. Separation can be accomplished by having the animal quarters in a separate building, wing, floor, or room. Careful planning should make it possible to place animal housing areas next to or near research laboratories but separated from them by barriers, such as entry locks, corridors, or floors. Additional considerations include the impact of noise and vibration generated from within the facility and from surrounding areas of the building, as well as security of the facility.

Animals should be housed in facilities dedicated to or assigned for that purpose, not in laboratories merely for convenience. If animals must be maintained in a laboratory to satisfy the scientific aims of a protocol, that space should be appropriate to house and care for the animals and its use limited to the period during which it is required. If needed, measures should be taken to minimize occupational hazards related to exposure to animals both in the research area and during transport to and from the area.

Centralization Versus Decentralization

In a physically centralized animal facility, support, care, and use areas are adjacent to the animal housing space. Decentralized animal housing and use occur in space that is not solely dedicated to animal care or support or is physically separated from the support areas and animal care personnel. Centralization often reduces operating costs, providing a more efficient flow of animal care supplies, equipment, and personnel; more efficient use of environmental controls; and less duplication of support services. Centralization reduces the needs for transporting animals between housing and study sites, thereby minimizing the risks of transport stress and exposure to disease agents; affords greater security by providing the opportunity to control facility access; and increases the ease of monitoring staff and animals.

Decentralized animal facilities generally cost more to construct because of the requirement for specialized environmental systems and controls in multiple sites. Duplicate equipment (e.g., cage washers) may be needed, or soiled materials may need to be moved distances for processing. But decentralization may be preferred for certain specialized research services such as imaging, quarantine, and proximity to research facilities, or for biosecurity reasons. Decentralization may be necessary to accommodate large or complex equipment, such as magnetic resonance imaging, or to permit space sharing by users from multiple facilities or institutions. The opportunity for exposure to disease agents is much greater in these situations and special consideration should be given to biosecurity, including transportation to and from the site, quarantine before or after use of the specialized research area, and environmental and equipment decontamination.

The decisions leading to selection of physically centralized versus decentralized animal facilities should be made early and carefully and should involve all stakeholders (NRC 1996; Ruys 1991).

FUNCTIONAL AREAS

Professional judgment should be exercised in the development of a practical, functional, and ef cient physical plant for animal care and use. The size, nature, and intensity of an institutional Program (see Chapter 2) will determine the speci c facility and support functions needed. In facilities that are small, maintain few animals, or maintain animals under special conditions—such as facilities used exclusively for housing gnotobiotic or speci c pathogen-free (SPF) colonies or animals in runs, pens, or outdoor housing—some functional areas listed below may be unnecessary or may be included in a multipurpose area.

Space is required for the following:

- animal housing, care, and sanitation
- receipt, quarantine, separation, and/or rederivation of animals
- separation of species or isolation of individual projects when necessary
- storage.

Most multipurpose animal facilities may also include the following:

- specialized laboratories or space contiguous with or near animal housing areas for such activities as surgery, intensive care, necropsy, irradiation, preparation of special diets, experimental procedures, behavioral testing, imaging, clinical treatment, and diagnostic laboratory procedures

- containment facilities or equipment, if hazardous biologic, physical, or chemical agents are to be used
- barrier facilities for housing of SPF rodents, especially valuable genetically modi ed animals, or irreplaceable animal models

becoming gouged, cracked, or pitted. Depending on their use, oors should be monolithic or have a minimal number of joints. Some materials that have

Power and Lighting

The electrical system should be safe and provide appropriate lighting, a sufficient number of power outlets, and suitable amperage for specialized equipment. In the event of power failure, an alternative or emergency power supply should be available to maintain critical services (e.g., the HVAC system, ventilated caging systems [Huerkamp et al. 2003], or life support systems for aquatic species) or support functions (e.g., freezers and isolators) in animal rooms, operating suites, and other essential areas. Consideration should be given to outfitting movable equipment for which uninterrupted power is essential (e.g., ventilated racks), with twist-lock plugs to prevent accidental removal from the power supply.

Light fixtures, timers, switches, and outlets should be properly sealed to prevent vermin access. Recessed energy-efficient fluorescent lights are commonly used in animal facilities. Spectral quality of lights may be important for some species when maintained in the laboratory; in these cases full spectrum lamps may be appropriate. A time-controlled lighting system should be used to ensure a uniform diurnal lighting cycle. Override systems should be equipped with an automatic timeout or a warning light storage areas. Refrigerated storage, separated from other cold storage, is

SPECIAL FACILITIES

Surgery

The design of a surgical facility should accommodate the species to be operated on and the complexity of the procedures to be performed (Hessler 1991; see also Appendix A, Design and Construction of Animal Facilities). The facility, including that used for rodents, by necessity becomes larger and more complex as the number and size of animals or the complexity of procedures increase. For instance, a larger facility may be required to accommodate procedures on agricultural species, large surgical teams, imaging devices, robotic surgical systems, and/or laparoscopic equipment towers. Surgical facilities for agricultural species may additionally require floor drains, special restraint devices, and hydraulic operating tables.

For most survival surgery performed on rodents and other small species such as aquatics and birds, an animal procedure laboratory is recommended; the space should be dedicated to surgery and related activities when used for this purpose, and managed to minimize contamination from other activities conducted in the room at other times. The association of surgical facilities with diagnostic laboratories, imaging facilities, animal housing, staff offices, and so on should be considered in the overall context of the complexity of the surgical program. Centralized surgical facilities are cost-effective in equipment, conservation of space and personnel resources, and reduced transit of animals. They also enable enhanced personnel safety and professional oversight of both facilities and procedures.

For most surgical programs, functional components of aseptic surgery include surgical support, animal preparation, surgeon's scrub, operating room, and postoperative recovery. The areas that support those functions should be designed to minimize traffic flow and separate the related nonsurgical activities from the surgical procedure in the operating room. The separation is best achieved by physical barriers (AORN 1993) but may also be achieved by distance between areas or by the timing of appropriate cleaning and disinfection between activities.

Surgical facilities should be sufficiently separate from other areas to minimize unnecessary traffic and decrease the potential for contamination (Humphreys 1993). The number of personnel and their level of activity have been shown to be directly related to the level of bacterial contamination and the incidence of postoperative wound infection (Fitzgerald 1979). Traffic in the operating room can be reduced by the installation of an observation window, a communication system (such as an intercom system), and judicious location of doors.

Control of contamination and ease of cleaning should be key considerations in the design of a surgical facility. The interior surfaces should be

and rats, especially valuable genetically engineered animals, and SPF animals of other species.

Barrier facilities typically incorporate airlock or special entries (e.g., air or wet showers) for staff and supplies. Staff generally wear dedicated clothing and footwear, or freshly laundered, sterile, or disposable outer garments such as gowns, head and shoe covers, gloves, and sometimes face masks prior to entry. Consumables, such as feed or bedding, that may harbor infectious agents are autoclaved or are gamma-irradiated by the supplier and surface decontaminated on entry. Drinking water may be autoclaved or subject to specialized treatment (e.g., reverse osmosis filtration) to remove infectious agents. Caging and other materials with which the animals have direct contact may be sterilized after washing before reuse. Strict operational procedures are frequently established to preclude intermingling of clean and soiled supplies and personnel groups, depending on work function. Only animals of defined health status are received into the barrier, and once they leave they are prohibited from reentering without retesting. Personnel entry is restricted and those with access are appropriately trained in procedures that minimize the introduction of contaminants.

Engineering features may include high-level filtration of supply air (e.g., HEPA or 95% efficient filters), pressurization of the barrier with respect to surrounding areas, and directional airflow from clean to potentially contaminated areas. Specialized equipment augmenting the barrier may include isolator cages, individually ventilated cages, and animal changing stations.

Detailed information on barrier design, construction, and operations has been recently published (Hessler 2008; Lipman 2006, 2008).

Imaging

In vivo imaging offers noninvasive methods for evaluating structure contamination between groups of animals, different animal species, or between animals and humans (if the device is used for both animal and human subjects) is possible because these devices may be difficult to sanitize (Klaunberg and Davis 2008; Lipman 2006). If the imaging resource is located outside the animal facility, appropriate transportation methods and routes should be developed to avoid inappropriate exposure of humans to animals in transit. If possible, animals should not be moved past offices, lunch rooms, or public areas where people are likely to be present.

As imaging may require the subject to be immobile, often for extended time periods during image acquisition, provisions should be made for delivery of anesthetics and carrier gas, the scavenging of waste anesthetic gas, and adequate animal monitoring (Balaban and Hampshire 2001). Remote storage of gas tanks is generally required in facilities where magnetic resonance (MR) scanners are used as the magnetic field requires ferrous materials to be kept a safe distance away from the magnet. Site selection of MR scanners requires special attention because of their weight, the fringe field generated (especially from unshielded magnets), and the impact of ferrous elements of the building structure or its components, especially those that are not static (e.g., elevators), as they may affect field homogeneity. Most MR scanners are superconducting and require the use of cryogens. Because cryogen boil-off can lead to asphyxiation of both personnel and animals, rooms with MR scanners or in which cryogen gases are stored must be equipped with oxygen sensors and a method for increasing room ventilation to exhaust inert gases during cryogen filling (Klaunberg and Davis 2008).

Many imaging devices, especially those designed for small animals, are self-contained and require no special physical plant considerations. Provisions should be made to locate the operating console away from imaging devices that emit ionizing or magnetic radiation. Imaging devices with components that are difficult to sanitize should be covered with a disposable or sanitizable material when not in use.

Whole Body Irradiation

Total body irradiation of small laboratory animals may be accomplished using devices that emit either gamma- or X-rays. Devices are usually self-shielded and, because of the weight of the shielding material, may require special site considerations. Devices with gamma-emitting sources are subject to regulations that require adherence to specific security, monitoring, and personnel clearance requirements (Nuclear Regulatory Commission 2008). The site selected for irradiators should also take into account whether they are to be used for animals and biologics, as well as the source and microbial status of the animals to be irradiated. Locating them in the animal facility may require access for personnel who would normally not require it or may necessitate bringing animals into a facility where they are not normally housed.

Hazardous Agent Containment

The goal of containment is to “reduce or eliminate exposure of laboratory workers, other persons, and the outside environment to potential hazardous

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Addendum

Guide for the Care and Use of Laboratory Animals Eighth Edition

ADDENDUM: LIST OF EDITORIAL CHANGES FROM THE PREPUBLICATION VERSION[1]

1. Page 22. Original sentence: “Personnel training should include information on laboratory animal allergies, preventive control measures and proper techniques for working with animals (Gordon et at. 1997; Schweitzer et al. 2003; Thulin et al. 2002).” “…early recognition and reporting of allergy symptoms” was added to clarify the guidance and re ect the cited references.

2. Page 31. Original sentence: “They should therefore be used, when available, for all animal-related procedures (NIH 2008; USDA 1997b).” The NIH reference was removed because it applies only to the NIH intramural animal research program.

3. Page 32. Original sentence: “Principal investigators conducting eld research should be knowledgeable of relevant zoonotic diseases, associated safety issues, and, when working in an international environment, any local laws or regulations that apply.” Compliance with laws and regulations applies to eld investigations irrespective of location, so “when working in an international environment” and “local” were deleted.

[1]Page numbers re ect placement of revisions in this report.

10. Page 107. Original sentence: “The Centers for Disease Control and Prevention enforces regulations to prevent the introduction, transmission, or spread of communicable diseases and regulate the importation of any animal or animal product capable of carrying a zoonotic disease.” Because USDA also has jurisdiction over imports, it was added to the sentence.

11. Page 107. Original sentence: “The US Fish3(e)-3(g)-3(e8-)-150(-3(e)-3( )-2

Appendices

APPENDIX
A

Additional Selected References

SUBJECT MATTER

USE OF LABORATORY ANIMALS
Alternatives
Ethics and Welfare
Experimental Design and Statistics
Research and Testing Methodology

PROGRAM MANAGEMENT
General References
Laws, Regulations, and Policies
Education
Monitoring the Care and Use of Animals
Occupational Health and Safety

ENVIRONMENT, HOUSING, AND MANAGEMENT
General References
Environmental Enrichment
Genetics and Genetically Modi ed Animals
Species-Speci c References—Environment, Housing, and Management
- Agricultural Animals
- Amphibians, Reptiles, and Fish
- Birds
- Cats and Dogs
- Exotic, Wild, and Zoo Animals

Nonhuman Primates
Rodents and Rabbits
Other Animals

VETERINARY CARE
Transportation
Anesthesia, Pain, and Surgery
Disease Surveillance, Diagnosis, and Treatment
Pathology, Clinical Pathology, and Parasitology
Species-Speci c References—Veterinary Care
Agricultural Animals
Amphibians, Reptiles, and Fish
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APPENDIX

B

U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training

The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires in vivo experimentation with a wide variety of animal species. Whenever U.S. Government agencies develop requirements for testing, research, or training procedures involving the use of vertebrate animals, the following principles shall be considered; and whenever these agencies actually perform or sponsor such procedures, the responsible Institutional Official shall ensure that these principles are adhered to:

I. The transportation, care, and use of animals should be in accordance with **the** Animal Welfare Act (7 U.S.C. 2131 et. seq.) and other applicable Federal laws, guidelines, and policies.[1]

II. Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.

III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered.

[1]For guidance throughout these Principles, the reader is referred to the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute for Laboratory Animal Research, National Academy of Sciences.

IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.

V. Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.

VI. Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.

VII. The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes

APPENDIX

C

Statement of Task

The use of laboratory animals for biomedical research, testing and education is guided by the principles of the Three Rs, replacement of animals where acceptable non-animal models exist, reduction in the number of animals to the fewest needed to obtain statistically s(y)-3nisti3(c)-3(t evidence, while maintaining the performance standards of the 1996 *Guide*. The committee will ensure that any recommendations in the *Guide* will be consistent with current Public Health Service Policy, the Animal Welfare Regulations, and the most recent Report of the American Veterinary Medical Association Panel on Euthanasia.

In addition to the published report, the updated *Guide* will be posted on the Internet in a pdf or equivalent format such that users will be able to search the entire document at one time.

APPENDIX

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About the Authors

Janet C. Garber (Chair), DVM, PhD, received her Doctor of Veterinary Medicine degree from Iowa State University and her PhD in pathophysiology from the University of Wisconsin. Her experiences have included infectious disease research at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), primate medicine and research, GLP device and materials evaluation, and transplantation immunology. Her current interests are in the areas of laboratory animal f3(w)-3(a)-T-3( )-98(i3(m)-3(a)e-3(a)-I32-3 disct 63( )-20( )-20( )-2s raise Il raise resear, (n)-3(o)-3(a)-3(b)-3marast ter misntiO7Dmt been associated with IACUCs at small, medium, and large institutions for over two decades and is familiar with the oversight of animal care and use programs. He has served on multiple study sections for both the NIH and DOD. Dr. Barbee also served as an Oxford, UK 2006 fellow (recipient, VCU Harris-Manchester Award) where he examined policies, training, and security issues related to animal care and use within the UK.

Joseph T. Bielitzki, MS, DVM, is Research Manager, University of Central Florida. Dr. Bielitzki has worked with non-human primates in the laboratory environment for 20 years. Over this period he has worked with macaques (pig-tail, long-tail, Japanese, rhesus, stump-tail), baboons (yellow, green and hybrids) squirrel monkeys, capuchin monkeys, mangabeys, gibbons, chimpanzees, orangutans, bonobos, and gorillas. In the area of non-human primates his area of expertise is in enteric diseases, nursery rearing, and colony management. He has also worked with mice and rats in a variety of international facilities. He was instrumental in the writing and acceptance of the NASA Bioethical Principles for the Use of Animals in Research (NPD 8910.1). He speaks frequently on IACUC function and the importance of ethics in the use of animals. His background includes experience in academia, industry, and government in the roles of attending veterinarian, program manager, and researcher.

Leigh Ann Clayton, DVM, is Director of Animal Health at the National Aquarium in Baltimore where she also chairs the Animal Welfare Committee. Dr. Leigh Clayton has worked in the zoo/aquarium field or the exotic pet medicine field exclusively since 2000. As she has worked with animals held in aquatics systems both in recirculating fresh and salt water, she is experienced in managing disease and accomplishing preventive health programs for fishes, amphibians, and reptiles as well as birds and mammals. She is a Diplomate of the American Board of Veterinary Practitioners (Avian). Dr. Clayton has routinely used her knowledge of nitrogen cycling and the basics of a variety of life support system designs to solve health issues in these captive settings and help ensure adequate animal health. She has served on the Executive Board of the Association of Reptilian and Amphibian Veterinarians, a role that allowed her to routinely liaise with leading researchers in the amphibian medicine field.

John C. Donovan, DVM, is President of BioResources Inc. Dr. Donovan has over 30 years' experience working as a veterinarian in biomedical research and is board certified by the American College of Laboratory Animal Medicine (ACLAM). After 7 years in the U.S. Army's Medical Research and Development Command, he spent 10 years at the National Institutes of Health, becoming the Director of the National Cancer Institute's Office of Laboratory Animal Science. He began his career in the pharmaceutical industry in 1994 as Senior Director of Worldwide Laboratory Animal Resources for Rhone Poulenc-Rorer Pharmaceuticals, leading to his position as Vice President of Laboratory Animal Science and Welfare for Aventis Pharmaceuticals in 1999. In 2001 he moved to Wyeth Pharmaceuticals where he was Vice President of BioResources until his retirement in 2007. During his career, Dr. Donovan served in numerous professional leadership positions including President of ACLAM and President of the Board of Directors of the Pennsylvania Society for Biomedical Research (PSBR). He also served on several boards including those of the National Association for Biomedical Research, ACLAM, PSBR, and the New Jersey Association for Biomedical Research.

Dennis F. Kohn, DVM, PhD, is Professor Emeritus of Clinical Comparative Pathology at Columbia University. He received his DVM from Ohio State University and a doctorate in Medical Microbiology from West Virginia University. He is board certified by the American College of Laboratory Animal Medicine. He has directed laboratory animal resource/comparative medicine programs at West Virginia University Medical Center, University of Texas Medical School at Houston, and the Health Sciences Division, Columbia University. His research interests have dealt primarily with the pathogenicity of *Mycoplasma pulmonis* in the respiratory tract of laboratory rats, and the experimental pathology induced within the CNS and joints of rats inoculated with *M. pulmonis*. He is a past president of the American College of Laboratory Animal Medicine and the American Society of Laboratory Animal Practitioners, and as chair of a number of American Association of Laboratory Animal Science committees. He has served as a Council member of AAALAC-International, as a member of the 1986 American Veterinary Medical Association's Panel on Euthanasia, and the 1996 Institute of Laboratory Animal Resources' committee to revise the *Guide*.

Neil S. Lipman, VMD, is Director of the Center of Comparative Medicine and Pathology serving the Memorial Sloan-Kettering Cancer Center (MSKCC) and the Weill Medical College of Cornell University and is Professor of Veterinary Medicine in Pathology and Laboratory Medicine at Weill Cornell as well as a Laboratory Member at the Sloan-Kettering Institute at MSKCC. Dr. Lipman is a Diplomate of the American College of Laboratory Animal Medicine with over 25 years' experience in laboratory animal medicine and science. Dr. Lipman has expertise in vivarium design, engineering, and operations, having designed over 1.5 million gross square feet of vivarium space and overseen the operation of a number of major academic animal resource programs. His research interests are principally translational and include development and analysis of new technologies especially with respect to rodent housing systems and monoclonal antibody production, the characterization of various animal models, understanding the etiopathogenesis of endocrinologic disorders affecting laboratory animal species, and development and analysis of novel therapeutic strategies. Throughout his career, Dr. Lipman has been extensively involved in the postgraduate training of laboratory animal specialists.

Paul Locke,MPH, JD, DrPH, an environmental health scientist and attorney, is Associate Professor at the Johns Hopkins University Bloomberg School of Public Health in the Department of Environmental Health Sciences, Division of Toxicology. He holds an MPH from Yale University School of Medicine, a DrPH from the Johns Hopkins University Bloomberg School of Public Health and a JD degree from Vanderbilt University School of Law. Prior to joining the Department of Environmental Health, he was the Deputy Director of the Pew Environmental Health Commission and the Director of the Center for Public Health and Law at the Environmental Law Institute. Dr. Locke's research and practice focus on how decision makers use environmental health science and toxicology in regulation and policy making and how environmental health sciences in uence the policy-making process. His areas of study include alternatives to animal testing in biomedical research, with particular emphasis on toxicity testing. He also maintains an active research program in radiation studies and radiation protection policy. Dr. Locke directs the Doctor of Public Health degree program in the Department of Environmental Health Sciences and is co-director of the Johns Hopkins certi cate program in Humane Science and Toxicology.

regulations concerning research animal care and use. Her research interests include innate immunity and infectious disease, toxicologic pathology, and the interactions between rodents and their environment as they relate to disease susceptibility. In 2007 she was the inaugural recipient of the North American Animal Welfare Award, co-sponsored by Procter & Gamble and the Humane Society of the United States.

Geoffrey A. Wood, DVM, PhD, DVSc, is Associate Professor in the Department of Pathobiology at the Ontario Veterinary College, University of Guelph, Canada. Dr. Wood has a doctorate in cancer biology and a doctorate in veterinary pathology. He has been involved in design or pathologic characterization of hundreds of genetically engineered rodents, both as the former Associate Director of Pathology at the Centre for Modeling Human Disease in Toronto, and in his current position. His lab conducts research on cancer genetics and the process of metastasis, with a focus on bone and prostate cancer. Dr. Wood's research collaborations include projects investigating various aspects of a wide range of different cancer types, as well as studies on stem cell biology, immunity, and in ammation.

Hanno Würbel, Dr.sc.nat, is Professor of Animal Welfare and Ethology at the Justus Liebig University in Giessen, Germany. He has studied biology (zoology) at the University of Berne, Switzerland and graduated from the ETH Zürich, Switzerland with a doctorate in natural sciences. He has experience in animal behavior and in the scienti c assessment of animal well-being, and has mostly worked with rodents, but also with rabbits, dogs, poultry, and horses. His research focuses on environment-dependent plasticity of brain and behavior in relation to questions of animal husbandry and animal welfare. In 2005 Dr. Würbel received the Hessian Animal Welfare Research Prize and in 2009 the Felix Wankel Animal Welfare Research Award. He is a member of the Animal Welfare Council of the German government, Central Animal Welfare Of cer of the University of Giessen, and head of the University's Central Animal Facility. He is also a council member of the International Society of Applied Ethology (ISAE), editor of the Journal of Applied Animal Welfare Science, and editorial board member of the journal Applied Animal Behaviour Science.

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