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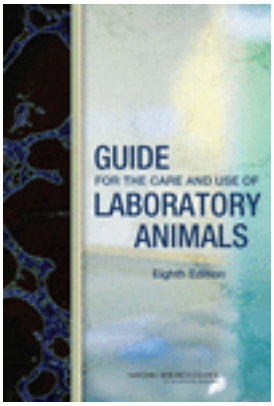

Guide for the Care and Use of Laboratory Animals: Eighth Edition

Committee for the Update of the Guide for the Care and Use of Laboratory Animals; National Research Council

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A respected resource for decades, the Guide for the Care and Use of Laboratory Animals has been updated by a committee of experts, taking into consideration input from the scientific and laboratory animal communities and the public at large. The Guide incorporates new scientific information on common laboratory animals, including aquatic species, and includes extensive references. It is organized around major components of animal use: Key concepts of animal care and use. The Guide sets the framework for the humane care and use of laboratory animals. Animal care and use program. The Guide discusses the concept of a broad Program of Animal Care and Use, including roles and responsibilities of the Institutional Official, Attending Veterinarian and the Institutional Animal Care and Use Committee. Animal environment, husbandry, and management. A chapter on this topic is now divided into sections on terrestrial and aquatic animals and provides recommendations for housing and environment, husbandry, behavioral and population management, and more. Veterinary care. The Guide discusses veterinary care and the responsibilities of the Attending Veterinarian. It includes recommendations on animal procurement and transportation, preventive medicine (including animal biosecurity), and clinical care and management. The Guide addresses distress and pain recognition and relief, and issues surrounding euthanasia.Physical plant. The Guide identifies design issues, providing construction guidelines for functional areas; considerations such as drainage, vibration and noise control, and environmental monitoring; and specialized facilities for animal housing and research needs. The Guide for the Care and Use of Laboratory Animals provides a framework for the judgments required in the management of animal facilities. This updated and expanded resource of proven value will be important to scientists and researchers, veterinarians, animal care personnel, facilities managers, institutional administrators, policy makers involved in research issues, and animal welfare advocates.

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Key Concepts

This edition of the *Guide for the Care and Use of Laboratory Animals* (the *Guide*) strongly affirms 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 scientific 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 researchers and their institutions. The use of laboratory animals in research, teaching, testing, and production is also governed or affected by various federal and local laws, regulations, and standards; for example, in the United States the Animal Welfare Act (AWA 1990) and Regulations (PL 89-544; USDA 1985) and/or Public Health Service (PHS) Policy (PHS 2002) may apply. Compliance with these laws, regulations, policies, and standards (or subsequent revised versions) in the establishment and implementation of a program of animal care and use is discussed in Chapter 2.

Taken together, the practical effect of these laws, regulations, and policies is to establish a system of self-regulation and regulatory oversight that binds researchers and institutions using animals. Both researchers and institutions have affirmative duties of humane care and use that are supported by practical, ethical, and scientific principles. This system of self-regulation establishes a rigorous program of animal care and use and provides flexibility in fulfilling the responsibility to provide humane care. The specific

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 many concepts throughout that may be helpful. Individual sections will be particularly relevant to certain users, and it is expected that the reader will explore in more detail the references provided (including those in Appendix A) on topics of interest.

Members of the scientific community (investigators and other animal users) will find Chapters 1 and 2 (and portions of Chapter 4) of the *Guide* useful for their interactions with the IACUC, attending veterinarian, and administrators regarding animal care as well as the preparation of animal care and use protocols. Scientific review committees and journal editors may choose to refer to multiple sections of the *Guide* to determine whether scientists contributing proposals and manuscripts have met the appropriate standards in their planned use of animals. The *Guide* can assist IACUCs and administrators in protocol review, assessment, and oversight of an animal care and use program. Veterinarians should find Chapters 3 through 5

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 point; readers are encouraged to go beyond these provisions. In certain situations, special considerations will arise during protocol review and planning; several of these situations are discussed in more detail in Chapter 2.

THE THREE Rs

The Three Rs represent a practical method for implementation of the principles described above. In 1959, W.M.S. Russell and R.L. Burch published a practical strategy of replacement, refinement, and reduction—referred to as the Three Rs—for researchers to apply when considering experimental

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).

Refinement refers to modifications of husbandry or experimental procedures to enhance animal well-being and minimize or eliminate pain and distress. While institutions and investigators should take all reasonable measures to eliminate pain and distress through refinement, IACUCs should understand that with some types of studies there may be either unforeseen or intended experimental outcomes that produce pain. These outcomes may or may not be eliminated based on the goals of the study.

Reduction involves strategies for obtaining comparable levels of information from the use of fewer animals or for maximizing the information obtained from a given number of animals (without increasing pain or distress) so that in the long run fewer animals are needed to acquire the same scientific information. This approach relies on an analysis of experimental design, applications of newer technologies, the use of appropriate statistical methods, and control of environmentally related variability in animal housing and study areas (see Appendix A).

Refinement and reduction goals should be balanced on a case-by-case basis. Principal investigators are strongly discouraged from advocating animal reuse as a reduction strategy, and reduction should not be a rationale for reusing an animal or animals that have already undergone experimental procedures especially if the well-being of the animals would be compromised. Studies that may result in severe or chronic pain or significant alterations in the animals' ability to maintain normal physiology, or adequately respond to stressors, should include descriptions of appropriate humane endpoints or provide science-based justification for not using a particular, commonly accepted humane endpoint. Veterinary consultation must occur when pain or distress is beyond the level anticipated in the protocol description or when interventional control is not possible.

KEY TERMS USED IN THE *GUIDE*

The Committee for the Update of the *Guide* believes that the terms set out below are important for a full understanding of the *Guide*. Accordingly, we have defined these terms and concepts to provide users of the *Guide* with additional assistance in implementing their responsibilities.

Humane Care

Humane care means those actions taken to ensure that laboratory animals are treated according to high ethical and scientific 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 of self-regulation it supports (Klein and Bayne 2007).

Animal Care and Use Program

The *animal care and use program* (the Program) means the policies, procedures, standards, organizational structure, staffing, facilities, and practices put into place by an institution to achieve the humane care and use of animals in the laboratory and throughout the institution. It includes the establishment and support of an IACUC or equivalent ethical oversight committee and the maintenance of an environment in which the IACUC can function successfully to carry out its responsibilities under the *Guide* and applicable laws and policies. Chapter 2 provides a more expansive discussion of the importance of the *Guide* and its application to animal care and use programs.

Engineering, Performance, and Practice Standards

Engineering standard means a standard or guideline that specifies in detail a method, technology, or technique for achieving a desired outcome; it does not provide for modification in the event that acceptable alternative methods are available or unusual circumstances arise. Engineering standards are prescriptive and provide limited flexibility for implementation. However, an engineering standard can be useful to establish a baseline and is relatively easy to use in evaluating compliance.

Performance standard means a standard or guideline that, while describing a desired outcome, provides flexibility in achieving this outcome by granting discretion to those responsible for managing the animal care and use program, the researcher, and the IACUC. The performance approach requires professional input, sound judgment, and a team approach to achieve specific goals. It is essential that the desired outcomes and/or goals be clearly defined and appropriate performance measures regularly monitored in order to verify the success of the process. Performance standards can be advantageous because they accommodate the consideration of many variables (such as the species and previous history of the animals, facilities, staff

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 procedures can assist an institution in complying with regulations, policies, and principles as well as with day-to-day operations and management.

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 specific decisions regarding animal care and use. Because the *Guide* is written in general terms, IACUCs have a key role in interpretation, implementation, oversight, and evaluation of institutional animal care and use programs.

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GUIDE
FOR THE CARE AND USE OF
LABORATORY ANIMALS

Eighth Edition

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

Institute for Laboratory Animal Research

Division on Earth and Life Studies

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Reviewers

This eighth edition of the *Guide for the Care and Use of Laboratory Animals* has been reviewed in draft form by individuals chosen for their diverse perspectives and expertise, in accordance with procedures approved by the Report Review Committee of the National Research Council. The purpose of this independent review is to provide candid and critical comments that will assist the Committee in making its published report as sound as possible, and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberation process. The Committee thanks the following individuals for their review of the draft report:

Michael B. Ballinger, Amgen
Philippe J.R. Baneux, PreLabs
Stephen W. Barthold, University of California-Davis
Linda C. Cork, Stanford University
Jann Hau, University of Copenhagen, Denmark
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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.

Preface

The purpose of the *Guide for the Care and Use of Laboratory Animals* (the *Guide*), as expressed in the charge to the Committee for the Update of the *Guide*, is to assist institutions in caring for and using animals in ways judged to be scientifically, technically, and humanely appropriate. The *Guide* is also intended to assist investigators in fulfilling their obligation to plan and conduct animal experiments in accord with the highest scientific, humane, and ethical principles. Recommendations in the *Guide* are based on published data, scientific principles, expert opinion, and experience with methods and practices that have proved to be consistent with both high-quality research and humane animal care and use. These recommendations should be used as a foundation for the development of a comprehensive animal care and use program, recognizing that the concept and application of performance standards, in accordance with goals, outcomes, and considerations defined in the *Guide*, is essential to this process.

The *Guide* is an internationally accepted primary reference on animal care and use, and its use is required in the United States by the Public Health Service Policy. It was first published in 1963, under the title *Guide for Laboratory Animal Facilities and Care*, and was revised in 1965, 1968, 1972, 1978, 1985, and 1996. More than 550,000 copies have been printed since its first publication.

In 2006 an ad hoc committee appointed by the Institute for Laboratory Animal Research recommended that the *Guide* be updated. The Committee for the Update of the *Guide for the Care and Use of Laboratory Animals* was appointed in 2008 by the National Research Council; its 13 members

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* expresses its appreciation to the Animal Welfare Information Center, National Agricultural Library, USDA, for its assistance in compiling bibliographies and references. This task would have been formidable without the help of the Center's staff. Appreciation is also extended to the reviewers of this volume, to Rhonda Haycraft for providing exemplary administrative and logistical assistance, and especially to Lida Anestidou, Study Director, who, through extraordinary patience, persistence, and scientific insight, managed the process from beginning to end.

Readers who detect errors of omission or commission are invited to send corrections and suggestions to the Institute for Laboratory Animal Research, National Research Council, 500 Fifth Street NW, Washington, DC 20001.

Janet C. Garber, *Chair*
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 five 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 Refinement—and provides an enhanced discussion of the ethics of animal use and investigator/institutional obligations.

Chapter 2 focuses on the overall institutional *animal care and use program* (Program), in addition to many of the topics previously covered in Chapter 1 of the seventh edition. It defines the evolved concept of Program and provides a framework for its intra-institutional integration, taking into account institutional policies and responsibilities, regulatory considerations, Program and personnel management (including training and occupational health and safety), and Program oversight. Discussions of the latter include institutional animal care and use committee (IACUC) functions, protocol and Program review, postapproval monitoring (a new section), and considerations such as humane endpoints and multiple survival surgical procedures. The Committee endorses the American College of Laboratory Animal Medicine's "Guidelines for Adequate Veterinary Care."

Chapter 3 focuses on the animals themselves and, unlike previous editions, addresses terrestrial and aquatic species in separate sections, reflect-

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 are separated in a new category. These changes were motivated by the Committee's recognition (affirmed in comments solicited from NHP experts) that these animals need more floor and vertical space, at least in some groups, to exercise their natural habits.

Chapter 4 discusses veterinary care and the responsibilities of the attending veterinarian. It introduces the concept of *animal biosecurity* and upholds its central role in ensuring the health of laboratory animals. The chapter includes recommendations relative to animal procurement, transportation, and preventive medicine, and expands the sections on clinical care and management, surgery (with a new section on intraoperative monitoring), pain and distress, and euthanasia.

Chapter 5 discusses physical plant–related topics and includes updated and new material on vibration control; physical security and access control; hazardous agent containment; and special facilities for imaging and whole body irradiation, barrier housing, behavioral studies, and aquatic species housing. The chapter provides detailed discussion of centralized versus decentralized animal facilities and introduces the concept of variable-volume HVAC systems with a nod toward energy conservation and efficiency.

Appendix A is the updated bibliography; Appendix B presents the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training; Appendix C presents the Statement

of Task; and Appendix D provides the biographical sketches of the Committee members.

In accordance with the Statement of Task ("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"), the *Guide* is available in searchable pdf format on the National Academies Press website, www.nap.edu.

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