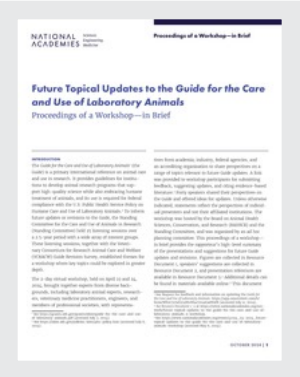

Future Topical Updates to the Guide for the Care and Use of Laboratory Animals: Proceedings of a Workshop—in Brief (2024)

DETAILS

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Proceedings of a Workshop—in Brief

Future Topical Updates to the *Guide for the Care and Use of Laboratory Animals*

Proceedings of a Workshop—in Brief

INTRODUCTION

The *Guide for the Care and Use of Laboratory Animals*[1] (the *Guide*) is a primary international reference on animal care and use in research. It provides guidelines for institutions to develop animal research programs that support high-quality science while also embracing humane treatment of animals, and its use is required for federal compliance with the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals.[2] To inform future updates or revisions to the *Guide*, the Standing Committee for the Care and Use of Animals in Research (Standing Committee) held 25 listening sessions over a 2.5-year period with a wide array of interest groups. These listening sessions, together with the Veterinary Consortium for Research Animal Care and Welfare (VCRACW) Guide Revision Survey, established themes for a workshop where key topics could be explored in greater depth.

The 2-day virtual workshop, held on April 23 and 24, 2024, brought together experts from diverse backgrounds, including laboratory animal experts, researchers, veterinary medicine practitioners, engineers, and members of professional societies, with representatives from academia, industry, federal agencies, and an accrediting organization to share perspectives on a range of topics relevant to future *Guide* updates. A link was provided to workshop participants for submitting feedback, suggesting updates, and citing evidence-based literature.[3] Forty speakers shared their perspectives on the *Guide* and offered ideas for updates. Unless otherwise indicated, statements reflect the perspectives of individual presenters and not their affiliated institutions. The workshop was hosted by the Board on Animal Health Sciences, Conservation, and Research (BAHSCR) and the Standing Committee, and was organized by an ad hoc planning committee. This proceedings of a workshop—in brief provides the rapporteur's high-level summary of the presentations and suggestions for future *Guide* updates and revisions. Figures are collected in Resource Document 1, speakers' suggestions are collected in Resource Document 2, and presentation references are available in Resource Document 3.[4] Additional details can be found in materials available online.[5] This document

[1] See https://grants.nih.gov/grants/olaw/guide-for-the-care-and-use-of-laboratory-animals.pdf (accessed July 2, 2024).
[2] See https://olaw.nih.gov/policies-laws/phs-policy.htm (accessed July 6, 2024).
[3] See Request for feedback and information on updating the *Guide for the Care and Use of Laboratory Animals*: https://app.smartsheet.com/b/form/8ffce7370d37486c8f4e7104d3a889f8 (accessed July 11, 2024).
[4] *See Resource Document 1–3* at https://www.nationalacademies.org/our-work/future-topical-updates-to-the-guide-for-the-care-and-use-of-laboratory-animals-a-workshop.
[5] See https://www.nationalacademies.org/event/42214_04-2024_future-topical-updates-to-the-guide-for-the-care-and-use-of-laboratory-animals-workshop (accessed May 6, 2024).

and accompanying Resource Documents highlight potential opportunities for action, but they should not be viewed as sources of consensus conclusions or recommendations of the National Academies of Sciences, Engineering, and Medicine.

HISTORICAL PERSPECTIVES ON THE *GUIDE*

Robert Dysko (University of Michigan) offered a brief history of the entity responsible for publishing the *Guide*, which was recently renamed as BAHSCR. James Fox (Massachusetts Institute of Technology) discussed the history of *Guide* updates and revisions. In Phase 1 of the current effort, the 13-member Standing Committee held listening sessions with a total of 355 individuals representing the broad array of professions and organizations involved in laboratory animal use and regulation, said Fox. A document summarizing these listening sessions is available online.[6] Phase 2 includes the April 2024 workshop, which was intended to inform the public on the content shared during the listening sessions and to collect input on topics for the development of the ninth edition of the *Guide*. Phase 3 will consist of a study by an ad hoc consensus committee that will write the ninth edition. In Phase 4, the Standing Committee will continue to explore areas for future updates (see Figure 1).

Janet Garber (DVM, PhD), who chaired the committee for the eighth edition of the *Guide*, offered insights for the current effort. Support for maintaining the concept of performance standards in the eighth edition of the *Guide* was reinforced during that consensus committee's public meetings, solicited written comments, and report review process, said Garber. In the eighth edition, Garber's committee added information to help users implement performance standards. For example, a discussion of cage space was expanded to include the requirement that animals "must have enough space to express their natural postures and postural adjustments…" Garber also highlighted the importance of practice standards, which enable procedures to be shared among institutions and to evolve over time in response to changing conditions and new information.

[6] See https://www.nationalacademies.org/our-work/standing-committee-for-the-care-and-use-of-animals-in-research (accessed August 29, 2024).

VCRACW *GUIDE* REVISION SURVEY RESULTS

Kate Storves (Intuitive Surgical) summarized the results of a 2022 VCRACW survey[7] of members of four large animal science societies that evaluated their preferences in revising the *Guide*. According to the VCRACW survey's 179 respondents, the five individual sections of the *Guide* most in need of revision are as follows, in descending order: Terrestrial Housing (an "overwhelming first," said Storves), Terrestrial Environment, Terrestrial Management, Role of the IACUC, and Aquatic Housing. Drilling down further, respondents were asked which "Topics" (highlighted subsections) were most in need of revision. The top 10 topics are listed in Figure 2.

Storves summarized the 531 responses to open-ended questions, which asked respondents to name the key issue(s) that could be revised in each chapter and to propose new sections or topics. Key themes in Chapter 1 were the use of must/should/may and harm–benefit analysis. The predominant concern in Chapter 2 was IACUC responsibilities, followed by disaster planning, compliance, and training. Comments on Chapter 3 addressed space requirements, environment, social housing, enrichment, cleaning, aquatics, and alternate caging systems. Chapter 4 responses focused on pain and distress, pathogen surveillance, euthanasia, and surgery and anesthesia, said Storves.

Many respondents suggested expanding the *Guide* to include additional guidance for cephalopods, other invertebrates, wildlife, client-owned animals, and/or "tertiary species,"[8] said Storves. Suggestions for new topics included contingency planning, involvement of the IACUC in study design, mental health, compliance, animal behavior, and adoption. Regarding the format of the *Guide*, most preferred either a static document with regular, defined review intervals or a hybrid document consisting of a static core with dynamic guidance documents in a wiki-like format.

Based on the listening sessions, the Standing Committee identified eight broad themes or challenges.

[7] See https://blog.primr.org/help-improve-the-guide/ (accessed July 30, 2024).

[8] Specialty colleges focused on laboratory animal medicine differentiate species into primary, secondary, and tertiary importance for their diplomates, based on the knowledge and skills required for specialty certification. See Figure S2 in Hedenqvist et al. (2022) for comparison of species to each college.

CHALLENGE 1: USING THE *GUIDE* FOR REGULATORY PURPOSES

The question of "whether or not [the *Guide*] is regulation" was raised frequently in the listening sessions, said Robert Sikes (University of Arkansas at Little Rock), who noted that it is viewed as "de facto regulatory" and therefore needs to harmonize with existing statutes, regulations, and other guidance resources. The listening session participants asked for "clear, unambiguous language to prevent over-interpretation from regulators," said Kelly Decker (U.S. Food and Drug Administration [FDA]).

NIH OLAW uses the *Guide* to implement the Health Research Extension Act of 1985,[9] which directs NIH to establish guidelines for the proper care and use of animals in biomedical and behavioral research, said Axel Wolff (NIH OLAW). IACUC inspections of animal facilities use the *Guide* as a basis for evaluation, while semi-annual IACUC reports must describe "the nature and extent of the institution's adherence to the *Guide*… [and] identify specifically any departures …and state the reasons for each," said Wolff. USDA does not use the *Guide* for inspections and enforcement, said Louis DiVincenti (USDA); it relies entirely on the Animal Welfare Act (AWA) and Animal Welfare Regulations (AWR).[10] However, USDA does draw on performance standards, which may come from documents like the *Guide,* for species that are not specifically addressed in the AWA/AWR, he added.

Must/Should/May

The most frequently mentioned topic at the listening sessions was defining "must," "should," and "may," said Sikes, who noted that "should" statements "tend to evolve into expectations." Michael Huerkamp (Emory University) described "should" as "a polite way of saying 'must' with less urgency and some flexibility." AAALAC International is "very reliant on the 'shoulds' and the 'musts'" for accreditation evaluations, said Debra L. Hickman (AAALAC International). If a unit is not doing something indicated as a "should" in the *Guide*, then AAALAC International might consider it a "suggestion for improvement." In contrast, everything indicated as a "must" in the *Guide* is mandatory for accreditation, she said.

USDA only uses "must" for actions required by legislation and regulation; "should" is used when the action is "strongly recommended but not specifically required," and "may" describes an action that is optional, said DiVincenti. The *Guide for the Care and Use of Agricultural Animals in Research and Teaching* (the Ag Guide)[11] uses "must" for "relatively few things that are very, very essential…access to water, limiting abuse, or rough handling," and "should" for "animal care and use [that] ought to be as indicated unless otherwise justified," said Cassandra Tucker (University of California, Davis); the word "recommend" is used to specify "an appropriate way of doing things but leaves room for other approaches that achieve the same result."

Stacy Pritt (Texas A&M University System) cautioned that the words "exception" and "departure" can have negative connotations and may seem to imply that institutions "are somehow falling short of *Guide* standards."

Regulatory Use of the *Guide* Inhibits Flexibility in Its Application

Several speakers stressed the importance of flexibility in the *Guide's* interpretation and application. However, the perception of the *Guide* as a regulatory instrument has caused many IACUCs to be hesitant to implement this approach, potentially stifling the use of professional judgment and science-based performance standards as promoted in the *Guide*.

CHALLENGE 2: USE OF THE *GUIDE*—THE REVIEW PROCESS

Several listening session participants expressed concern that the current review process overburdens both IACUCs and principal investigators (PIs), said moderator Katherine Thibault (National Ecological Observatory Network, Battelle).

The Increasing Burden on IACUCs and PIs

During the listening sessions, questions regarding what responsibilities fall within the purview of IACUCs were raised frequently, said Susan Harper (National Institutes of Health [NIH]). Several participants felt that IACUCs might be asked to address a growing list of issues that exceeds the expertise of committee members and would place an undue burden on them. Such issues included whether IACUCs should evaluate the experimental design, statistical rigor, scientific merit, and ethical soundness

[9] Public Law 99-158, sec. 495. See https://olaw.nih.gov/policies-laws/hrea-1985.htm (accessed July 2, 2024).
[10] See https://www.aphis.usda.gov/media/document/17164/file (accessed July 2, 2024).
[11] See https://www.asas.org/docs/default-source/default-document-library/agguide_4th.pdf?sfvrsn=56b44ed1_2 (accessed July 6, 2024).

of experiments, and should address questions relating to occupational safety. In response, IACUCs have found it necessary to modify their deliberative process and reassign some functions to subject matter experts (SMEs). While this restructuring has taken several forms, Harper and Sikes suggested an approach in which researchers, IACUCs, and SMEs work together as equal partners serving distinct but overlapping functions, with the welfare of the animals as their shared goal (see Figure 3). Speakers considered how Certified Professional IACUC Administrators[12] might relieve some of the burden on IACUCs—for example, by providing continuing education and training.

Reinvigorating the 3Rs

The 3Rs (replacement, refinement, reduction) were developed as "a key conceptual framework" that sought to incorporate social concerns into the design of animal research, said Patricia V. Turner (University of Guelph). Over time, she said, this goal has stagnated among "a loss of individual responsibility and a sense of waiting for something external to happen to move lab animal science forward." Inspired by the NC3Rs'[13] update of these terms (see Figure 4), Turner suggested reinvigorating the concept of the 3Rs in the *Guide* by emphasizing the active responsibility of the institutions and individuals working with animals (i.e., to focus on training and education for implementation of new requirements).

Speaking as a translational scientist, Joe Kornegay (DVM, PhD), pointed to the low rate of translation of preclinical efficacy and adverse effects studies and a need for increased rigor and validation of animal experiments and models in the *Guide*. He also stressed the importance of applying a culture of care across research programs.

Defining Ethical Review and Animal Welfare

Ethical review of animal research is primarily the responsibility of the IACUC, said Kornegay, but whether IACUC review constitutes a full ethical review "can be debated," said Pritt. "Evaluating how the 3Rs are implemented… [is] not the same as a really robust and concrete ethical review of the proposed work itself," agreed Monika Burns (Novartis). Philippe Baneux (consultant), pondered that veterinarians are schooled in ethics but bioethicists have carved out a separate domain, so the answer may depend on how ethics is defined. Pritt suggested expanding the discussion of ethics beyond the 3Rs and defining "animal welfare." Without a clear definition, she warned, "readers and regulators will [use] their own definition…[that] may actually vary from the intent of the *Guide*."

A Culture of Care Considers Human as well as Animal Welfare

"The key to optimizing animal welfare is developing…a culture of care," said Taylor Bennett (National Association for Biomedical Research). Despite infrequently mentioning "culture of care," Kornegay said that the current *Guide* references its principles: "Both researchers and institutions have affirmative duties…to ensure that laboratory animals are treated according to high ethical and scientific standards." Bennett, Kornegay, and Turner suggested expanding the definition of "culture of care" to include the welfare of staff, creating an environment that nurtures compassion, supports open communication, and empowers staff to express their concerns.

For a program to work effectively, Bennett said, IACUCs and attending veterinarians (AVs) must take the lead in creating an environment of cooperation that makes it easy for the investigators to do their work—one in which "IACUCs and AVs are seen as part of the solution and not part of the problem" so "investigators will not only listen to them but seek them out when they need help."

The eighth edition of the *Guide* was innovative in its emphasis on training, said Huerkamp. However, he said that funding is a significant challenge to the care of research animals, with indirect costs failing to keep pace with rapidly increasing administrative costs related to training, occupational health, and program administration requirements. Another challenge is the tight labor market, which has driven Huerkamp's program and some peers to rely on automation and the use of lean management principles in many animal husbandry activities to contain costs and compensate for a shortage of workers. In brief, rising program costs paired with labor shortages have placed increased demands on staff working with research animals, potentially creating a toll on the culture of care and resulting in further loss of key staff.

Feedback from Industry Stakeholders

Industry uses the *Guide* to inform both on-site ("internal") and outsourced ("external") animal research programs, said Burns. Regarding "must/should/may,"

[12] See https://primr.org/cpia/ (accessed September 12, 2024).
[13] See https://www.nc3rs.org.uk/who-we-are/3rs (accessed July 2, 2024).

many stakeholders suggested replacing "should" statements with "may" statements, "pair[ed] with an expectation that the facility will provide data to justify [its] practices," said Burns. She added that the *Guide* "should address animal reduction by implementing good scientific and statistical practices." Next, Burns highlighted the risks of not updating the *Guide*, noting that new documents, such as the 2022 Marseille Declaration,[14] have been generated to fill gaps in the current *Guide* standards.

CHALLENGE 3: PERFORMANCE AND ENGINEERING STANDARDS

Jeffrey Everitt (Duke University) noted "overwhelming stakeholder support" for performance-based standards upheld by professional judgment and a desire for explicit language allowing for "significant flexibility" regarding how standards are met at each institution.

Performance Standards Are Preferred, with Caveats

"There's always going to be some engineering standards, but the day-to-day operations must be able to be tailored to the institution, and that requires performance standards," said Bennett, with many other speakers expressing similar views. BMBL6 distinguished between "performance" and "prescriptive" standards, and "where we could, we erred on the side of performance-based," said Paul Meechan, a biorisk consultant.

Huerkamp cautioned against "the engineering of performance standards," such as NIH OLAW expecting that mouse pups be accurately counted at birth. Each institution that tries to depart from engineering standards must conduct experiments to obtain persuasive data, he added, with no apparent benefit to research or animal welfare and suppressed innovation. The biggest challenge with performance standards is gauging compliance, said DiVincenti, and "ensuring that we are regulating consistently."

Panelists considered how a move entirely to performance standards could impact the rigor and reproducibility of the science. The issue of reproducibility is still evolving, said Bennett, who noted that minor facility issues, such as changes in personnel, can impact outcomes, as can the microbiome. Meechan encouraged the use of published methodologies to validate performance. Given the strong desire for outcome- and performance-based standards, several stakeholders wanted better ways to share information that could relieve the need to validate approaches anew for each institution, said Everitt, who suggested developing repositories for performance-based approaches.

Practice Standards

Practice standards are used to supplement the *Guide* with information based on what people in the field are doing, said Kathleen Pritchett-Corning (Harvard University), and they "tend to come into play where we are venturing into parts unknown" (e.g., when cephalopods or honeybees become research subjects, and definitive sources of information are unavailable).

Compliance Unit Standard Procedures (CUSP): A Database for Practice Standards

The CUSP database,[15] which is currently in development, "will allow institutions to share standard procedures that are used in animal research protocols" without having to validate them anew in each institution, said Aubrey Schoenleben (University of Washington). CUSP could be used to support a living version of the *Guide*.

Standards versus Guiding Principles

Steve Niemi (Boston University) said that standards "are presumed to apply to more than one situation, more than one institution, [and] more than one need." But *Guide* standards can also be wrong, he said: "We have this false premise that today's standards, of any kind, are equal to and sufficient for quality and…welfare," and this "impedes our mission." Instead of standards, Niemi suggested that the *Guide* offer "guiding principles" that "summarize ethical guidelines and societal expectations, avoid prescriptive or engineering standards, and rely on knowledgeable local oversight."[16]

Water Consumption as an Indicator of Health

Mark Churchland (Columbia University) described an approach to monitoring animals' health that "has the flexibility that you want from performance standards while still having the precision [of] engineering standards." Churchland trains rhesus monkeys to perform a wide variety of tasks, and he's found that each monkey

[14] See https://www.sanofi.com/assets/dotcom/content-app/documents/Marseille-Declaration-2022-signed.pdf (accessed July 2, 2024).

[15] See https://thefdp.org/demonstrations-resources/cusp/ (accessed July 9, 2024).

[16] Niemi cited U.S. Government *Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* that "have been in practice for many years [and] pretty much [cover]…all the elements" of this workshop. See https://olaw.nih.gov/policies-laws/gov-principles.htm (accessed May 30, 2024).

has a typical daily working water consumption (WWC). By tracking a monkey's weight and WWC daily, researchers can closely monitor its health and behavior.

CHALLENGE 4: KEY TOPICS IN HOUSING AND HUSBANDRY

Harper suggested that housing options should align with species' natural behaviors, life stage, and enrichment preferences. Any changes should be based on "scientific evidence that clearly shows a net gain in animal comfort or welfare."

Standards for Housing Rodents

Laboratory mice are domesticated animals with a behavioral plasticity comparable to that of humans, who can adapt to a wide variety of conditions. In studies performed by Pritchett-Corning and Brianna Gaskill (Novartis Institutes for Biomedical Research), mice and rats did not perform differently at either half or double the density recommended by the *Guide* (Gaskill and Pritchett-Corning, 2015a,b). She encouraged participants not to look at performance standards "as a way to bring out every last drop of efficiency in a system but…to allow us to work differently with respect, and respecting the telos of the animals we work with."

Poor Welfare Leads to Poor Science

Environmental stress on animals has been found to account for as much as 42 percent of data variability, said Gaskill, who highlighted some of the top environmental factors that cause stress in laboratory animals (Chesler et al., 2002). These include light, temperature, enrichment, handling, physical restraint, noise, vibration, social needs, and bedding. Vivaria do not provide ultraviolet light, which rodents use to detect urine markings, and complete darkness is unnatural and disrupts their circadian rhythms. The *Guide*'s recommended housing temperature for rodents is below their lower critical temperature, said Gaskill, leading to a 50–60 percent increase in metabolic rate and altering their immune function, reproduction, bone mineral density, and other physiological parameters. In addition to the ethical benefits of enrichment, studies show that enriched environments impact brain health, aging, immunity, and cancer, she said, indicating that enrichment "is important for the validity of our science."

"The impact of basic handling stress is undervalued and ingnored," said Gaskill. Citing work from the RISE Institute in Sweden,[17] she noted the difference in laboratory rodent behavior and its "astounding" implications for welfare when animals are trained and habituated to interact with humans. For the entire range of environmental stressors, "ultimately, it comes down to much control we are giving them over these stressors," she said. Overall, said Gaskill, the Guide should aim for refinement by "provid[ing] more positive experiences for animals" and not merely eliminating negative ones.

Non-Human Primate (NHP) Housing and Husbandry

The field of NHP housing and husbandry has grown tremendously since the *Guide* was last issued, and incorporating this growth into the *Guide* will advance both NHP welfare and biomedical research, said Mollie Bloomsmith (Emory University). Six key areas of progress include social housing, enrichment, animal training, housing, behavioral assessment, and behavioral staff. Bloomsmith noted "a consistent finding that compatible social housing improves behavior, reduces stress…and improves their clinical health." By reducing stress, she said, social living may also improve the "repeatability, reproducibility, and external validity" of NHP biomedical research. Similarly, positive reinforcement training of NHPs improves the ease of conducting biomedical research and increases the validity of the results by reducing stress as a confounder, she said. Environmental enrichment increases animals' coping by promoting a variety of species-typical behaviors, and using technology such as computer tablets can improve welfare—for example, by providing opportunities for cognitive challenge requiring monkeys to learn to solve problems with increasing difficulty over time.

Behavioral Performance Standards for Housing Diverse Species

GlaxoSmithKline (GSK) is using behavioral performance standards to develop a global system of animal housing and handling, said Mary Ann Vasbinder (GSK). For dogs, these standards include the ability to interact with other dogs and humans, to exercise and play, to hide, to engage in mentally and sensory stimulating activities, to chew, to eliminate in a designated area, and others. Similar performance standards have been developed for mice, rats, rabbits, minipigs, and macaques.[18] Vasbinder

[17] See https://www.ri.se/en/what-we-do/expertises/3r-focus-on-animal-welfare (accessed June 17, 2024).
[18] Vasbinder recommended the Disney Animal Enrichment website with its S.P.I.D.E.R. framework, which emphasizes continual documentation of animal behavior and reevaluation. See http://www.animaltraining.org/spider (accessed July 1, 2024).

showed examples of social housing, sleeping arrangements, and exercise areas that were developed for young beagles. Older dogs may have different needs.

Housing Aquatic Species

The diversity of aquatic species used in research is immense, said Raphael Malbrue (University of Virginia [UVA]). Laboratories at UVA study Xenopus, wrasses, clown fish, electric fish, crayfish, guppies, and axolotls, he said, and each one has unique requirements for life support, water quality, feeding, and housing. Given this diversity, the *Guide* should support performance-based standards for aquatic housing and husbandry, said Malbrue, and practices should be routinely evaluated.

CHALLENGE 5: GLOBAL IMPLICATIONS OF THE *GUIDE*

Given the international reach of the *Guide* and its use as a standard for accreditation by AAALAC International, it is critical that the *Guide* be able to articulate with other global standards, said Sikes.

Gaps in the *Guide*: Implications for Industry

In the years since the *Guide* was last updated, gaps have developed and been filled by other guidance documents, such as the 2022 Marseille Declaration. The existence of multiple standards around the world raises questions of whose standards should apply.[19] To maintain consistent science-based practices, Turner said, updating the *Guide* is particularly urgent for facilities that work with a global array of clients.

AAALAC International: Plugging the Gaps

AAALAC International[20] is a voluntary accreditation organization with more than 1,000 accredited units in 50 countries around the world, said Hickman. The eighth edition of the *Guide* currently serves as one of AAALAC's three primary standards of accreditation, but "we do not necessarily accept all of these standards at face value," she said, noting that AAALAC has published a handful of position statements to clarify how certain standards should be applied as well as a larger collection of frequently asked questions (FAQs).

AAALAC International established the Committee on Accreditation Standards "to fill some gaps that were identified" due to the length of time since the last *Guide* update, said Gary Borkowski (AAALAC International). Five subcommittees are preparing draft position statements related to culture of care, veterinary care, the 3Rs, housing conditions, and reference resources, he said.

CHALLENGE 6: EMERGING ISSUES FOR THE *GUIDE*

The listening sessions highlighted the importance of guidance to address the care and use of wildlife, pets, and diverse organisms in research, said Harper. Many stakeholders expressed a particular interest in compassion fatigue, said Douglas Brining (University of Texas Medical Branch at Galveston), although participants disagreed regarding the extent to which occupational health falls within the scope of the *Guide*.

Retirement, Rehoming, and Release

Retirement, rehoming, and release constitute the "fourth R" of animal research, said Laura Conour (Princeton University). FDA regulations changed to permit certain research animals to be retired or rehomed in 2019 (Buchino, 2020), and states have begun to legislate mandatory adoption laws requiring healthy research dogs or cats to be released to the public.[21] Retirement and rehoming programs can help relieve compassion fatigue and provide good public relations for the institution, said Conour, but they cannot be funded with federal grant money. For species that cannot be adopted, Conour offered advice for choosing a sanctuary and optimizing an animal's welfare during and after transition. Conour also touched on considerations for releasing wildlife back into the environment.

Occupational Health and Safety Considerations

Two sections of the *Guide* speak to "psychological occupational health and safety," said Sally Thompson-Iritani (University of Washington). Regarding "Personnel Security," she said, "many people [who work with research animals] live in constant fear of harassment for doing their jobs." Regarding "Investigating and Reporting Animal Welfare Concerns," she said, "people involved in our profession often live in fear of reporting concerns and being retaliated against." She suggested adding a mental health component to occupational health and safety programs to address both issues.

[19] For example, Turner noted that the Canadian Council on Animal Care's rat guidelines apply to Canadian facilities conducting work for companies located elsewhere.

[20] See https://www.aaalac.org/about/what-is-aaalac/ (accessed July 6, 2024).

[21] See, for example, https://www.animallaw.info/statute/mn-research-animals-135a191-research-dogs-and-cats#:~:text=Summary%3A%20This%20Minnesota%20law%20states,to%20an%20animal%20rescue%20organization. (accessed July 2, 2024).

The human–animal bond, and the stress it can cause when animals are in pain, in distress, or euthanized, is not covered in the current *Guide*, said Thompson-Iritani. Targeted training is required for physicians, veterinarians, and researchers to provide occupational health services to workers at the human–animal interface, she said.[22] Responsibility for maintaining a culture of care rests with the organization, and ultimate responsibility may rest with the institutional official, she said.

Occupational Health Risks in Animal Research

In the context of this workshop, said Tara Martin (University of Michigan), compassion fatigue may be defined as the "physical, emotional, and psychological depletion associated with working and caring for animals used in research" (Van Hooser et al., 2021) and can be thought of as a combination of burnout and secondary traumatic stress. Burnout may result from chronic occupational stress operating in a vicious cycle that can lead to emotional exhaustion and depression (see Figure 5). Secondary traumatic stress is the feeling of distress that comes from witnessing or causing harm to animals, including euthanasia. Workplace culture is a key contributor, as is a lack of training, exposure to animal suffering and death, feeling unable to provide appropriate animal care, and feeling locked out of decision-making. Social support is "a crucial mitigating factor for compassion fatigue," said Martin, as is communication from leadership, feeling valued for one's work, and understanding the research.

"Compassion fatigue and burnout are occupational health risks" in the field of animal research and should be included in an occupational health and safety program, said Patrick Lester (University of Michigan). This should be done via a risk-based institutional approach, he said, and it requires education and training. It is best handled through peer support by people who understand animal care, said Thompson-Iritani and Martin.

Companion Animal Research

The *Guide* does not address research on companion animals, but perhaps it should, said Kristen Weishaar (Colorado State University). Unlike laboratory animals, companion animals experience idiosyncratic and uncontrolled housing, watering, and feeding environments, as well as significant genetic heterogeneity and variable comorbidities. Informed consent is a crucial feature for research on companion animals, she said.[23] It is important for researchers to ensure that procedures are feasible in a clinical setting, that incentives are appropriate and not coercive, and that conflicts of interest are disclosed to clients. Some of this is mitigated by implementation of a clinical review board or veterinary clinical studies committee, which cooperates with the IACUC to review the research, she added.

Weishaar highlighted the Clinical and Translational Science Award One Health Alliance SMART IACUC[24] program, which enables the academic institution that is running a clinical trial to include other institutions in its study without requiring individual review by each one's IACUC.

CHALLENGE 7: FORMAT OF THE *GUIDE*

Striking the word "laboratory" from the title of the *Guide* could expand its utility from roughly two dozen laboratory species to a menagerie encompassing "about 70,000 species of vertebrates" plus cephalopods and other invertebrates, said Sikes. Rather than address all these taxa directly, the *Guide* likely would be restructured to reference multiple accessory guidance documents.

The Standing Committee is considering new platforms that could increase the accuracy, usability, and accessibility of the *Guide* by enabling regular updates, said Fox. Making the *Guide* or portions of it a living document is crucial to keep up with technology, fulfill the obligation to enhance animal welfare, "and uphold the privilege of conducting research," said Szczepan Baran (VeriSIM Life).

Niemi suggested moving the entire *Guide* to the internet and updating it continuously. Pritchett-Corning objected to a purely electronic *Guide* for reasons of version control and access, though she supported more frequent and reliable updates, while Pritt noted that IACUCs may have trouble working within online protocol templates.

To keep the Canadian Council on Animal Care (CCAC) *Guide to the Care and Use of Experimental Animals*[25] relevant between

[22] See https://deohs.washington.edu/nwcohs/training-programs/cohr (accessed July 9, 2024).

[23] Weishaar cited draft FDA guidance on informed consent for studies that enroll client-owned companion animals. See CVM GFI #282 Informed Consent Forms for Studies that Enroll Client-Owned Companion Animals, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-282-informed-consent-forms-studies-enroll-client-owned-companion-animals (accessed July 5, 2024).

[24] See https://ctsaonehealthalliance.org/2023/09/27/smart-iacuc-network/ (accessed July 6, 2024).

[25] See https://ccac.ca/Documents/Standards/Guidelines/Experimental_Animals_Vol1.pdf (accessed July 6, 2024).

updates—recognizing that different scientific areas progress at different rates—CCAC broke its guidance into multiple documents that could be updated separately, said Turner. The CCAC guidelines rely heavily on performance-based approaches. CCAC varies its timelines for implementation according to the type of change that is required.

Noting the discomfort of VCRACW survey participants with a fully living *Guide*, Thompson-Iritani and Schoenleben suggested a format comprising both static and dynamic portions. This format would divide the *Guide's* material into two parts: the fundamental framework (static and printable, with "musts") and living appendices (with "shoulds" and "mays"). The appendices would be in a dynamic, searchable, online format that is updated regularly to stay current with the literature, said Thompson-Iritani. These living appendices would each focus on a specific topic (such as animal welfare, occupational health, IACUC, wildlife, facilities, and atypical species) and would rely on SMEs and working groups for updating and review.

The *Guide* could be a "resource," said Zoltan Varga (University of Oregon), offering the example of the Zebrafish International Resource Center.[26] Varga suggested keeping a hard copy *Guide* as the "umbrella" over an online resource and turning the online PDF into a searchable book (see Figure 6). In light of the potentially vast amount of information that would be contained in any central relational database, Varga said, "the community of animal welfare professionals needs to develop a controlled common language—a care and welfare ontology."

As one example of how an accessory document might be maintained and kept current, Cia Johnson (American Veterinary Medical Association [AVMA]) discussed the *AVMA Guidelines for the Euthanasia of Animals*,[27] which is currently in its ninth edition (2020). For its most recent update, the AVMA convened numerous technique- and species-focused working groups, whose members created draft content in their areas of expertise. Chairs of the working groups formed a panel, and each panel edits the working group's drafts into a guidance document. To keep guidance on humane endings "living," all AVMA members can comment on the online document at any time, said Johnson. AVMA staff and working group members continually review the literature and comments, making minor updates through interim revisions.

Tucker discussed the *Ag Guide*, which is currently in its fourth (2020) edition. The *Ag Guide* is divided into two sections: one containing general information that applies across all agricultural species and one consisting of species-specific chapters for the most commonly used species. The fourth edition of the *Ag Guide* focused on animal-based outcomes "that quantify the animal's response to [its] environment" rather than a prescriptive approach to facility design or management procedures, said Tucker, because "we believe that there are many paths to ensuring animal welfare." Oversight by IACUCs and others is essential to evaluate if these approaches are successful, she added. Major strengths of the *Ag Guide*, said Tucker, include its authors' species-specific expertise, the emphasis on science-based best practice, the regular cycle of revision with both peer and public review, and the fact that it is widely and freely available.

Accessory reference documents will enable the *Guide* to focus on "humane principles, performance standards, and professional judgement" while remaining a reasonable length and not getting overly prescriptive, said Jori Leszczynski (University of Colorado Anschutz Medical Campus). These documents can allow the *Guide* to remain up-to-date and expand its scope to include a broad array of species. However, it may be important to limit and define what qualifies as an accessory reference document. Leszczynski identified 13 entries in the current *Guide* bibliography that might qualify as "true accessory reference documents," including seven taxon-specific guidance documents, such as the *Ag Guide*, and six documents related to more general aspects of animal care, such as the *AVMA Guidelines for the Euthanasia of Animals*. Regarding validation of these documents, she suggested "err[ing] on the side of respecting expertise." The ability to stay current through these accessory reference documents can keep the *Guide* "living" without raising the challenges of version control that would result from making it a continuously updatable online document, she said.

IACUCs face considerable challenges dealing with field research, which has a very different set of interests from biomedical research, even to the point of using different statistical approaches to determine how many animals

[26] See http://zebrafish.org (accessed July 2, 2024).
[27] See https://www.avma.org/sites/default/files/2020-02/Guidelines-on-Euthanasia-2020.pdf (accessed July 9, 2024).

to study, said Paul Stapp (California State University, Fullerton). IACUC oversight of field research is further challenged by the diversity of wild vertebrates and the low representation of field biologists on IACUCs. The current *Guide*'s structure, which pools birds, herps, and fish together with exotic species, is "an outdated way of looking at wildlife," he said. Stapp suggested giving the taxonomic guidelines primacy, particularly in the field. "We really need to continue to advocate for flexibility" in IACUCs and to foster a non-adversarial culture of partnership between IACUCs and PIs, he said, emphasizing that "fish and wildlife biologists are very interested in the resource…and we have a natural inclination to use humane and ethical methods."

CHALLENGE 8: MANAGING PROGRAMS OF THE FUTURE

Regarding the future direction of animal husbandry, many listening session participants emphasized the importance of managing energy demands efficiently, promoting sustainability, and staying current with evolving methods and technologies, said Harper.

The heating, ventilation, and air-conditioning (HVAC) system "is probably the single most expensive component of an animal facility," said Neil Lipman (Memorial Sloan Kettering Cancer Center). The HVAC system keeps the macro-environment under control by ensuring consistent and appropriate temperature, humidity, pressurization, and oxygen, as well as filtering out carbon dioxide (CO_2), particulates, and volatile contaminants. The eighth edition of the *Guide* requires 10–15 air changes per hour (ACH), which is a historic standard going back to the first edition in 1963, said Lipman. For each air change, fresh air enters the HVAC system at ambient temperature, is filtered and brought to the desired temperature and humidity, passes through the facility once, and is exhausted, in what is a very energy-intensive process.

In a constant volume ventilation system, which is what most vivaria use, a consistent amount of air enters and leaves the room, said Lipman. In the more practical variable air volume system, the amount of air flow is primarily a function of room temperature, with offsets in flow to maintain the desired pressure. Modern demand-controlled ventilation (DCV) systems use sensors to detect substances like CO_2, particulates, and volatile organic compounds and modulate air flow to maintain them within certain levels; this enables the facility to operate at a lower base air exchange rate, he said. This leads to a substantial reduction in the amount of air used, delivering considerable energy efficiencies and cost savings with no adverse impacts on the macro-environment, animal welfare, research staff, or scientific studies, he added.

Ventilation systems in vivaria must both control airborne hazards and satisfy general requirements related to indoor air quality, said Thomas C. Smith (3Flow). The risks vary within vivaria, which contain spaces designed for diverse tasks ranging from animal housing to office work. To derive operating specifications for laboratories, 3Flow helped develop a laboratory ventilation risk assessment (LVRA) (see Figure 7). The LVRA offers a way to evaluate the activities in multiple laboratories, assign the level of risk within each space, and determine the appropriate ventilation. Smith suggested developing a comparable vivarium ventilation risk assessment (see Figure 8). To enable the assessment of risk in a given space, Smith and his colleagues developed a tool to characterize the room ventilation effectiveness of the ventilation and ACH. Current standards established by ASHRAE[28] and the American Society of Safety Professionals[29] indicate that prescriptive ACH is "inappropriate," added Smith, who noted that not all spaces operating at the same ACH will provide an equivalent level of protection.

Higher ACH can even increase harm by creating turbulence that traps a contaminant in the breathing zone. Kishor Khankari (AnSight LLC) used computational fluid dynamics to develop a measure of ventilation effectiveness, Spread Index, which describes the precise areas of a room that would become occupied by any given contamination event. He demonstrated how this could be used to design the placement of ducts and vents to maximize the thermal comfort of people and animals while minimizing exposure to contaminants.

Baran described several ways that technology can be used to promote refinement and/or reduction.[30] Digital bio-

[28] See https://www.ashrae.org/technical-resources/standards-and-guidelines(accessed September 12, 2024).
[29] See https://tsi.com/learn/blog/quick-guide-to-ansi-asp-z9-5-2022-laboratory-ventilation (accessed September 12, 2024).
[30] The following U.S. Government *Principles for Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* can be addressed by digital technologies, said Baran: consideration of alternatives to animals, relevance to human health, minimizing the number of animals and their distress, establishing humane endpoints, and providing adequate veterinary care.

markers provide objective assessments that have clinical relevance, operational efficiencies, and computational accessibility, he said (see Figure 9). This enables the collection of more holistic animal-centric data without requiring handling, which can impact behavior. Digital biomarkers that align with histopathology can reduce the need to euthanize animals at multiple time points. Digital technologies are also increasingly relevant to the third R, replacement, he said (see Figure 10).

REFLECTIONS

Jennifer Lofgren (Novartis) highlighted topics that may benefit from further discussion as the project moves into Phase 3, including harm–benefit evaluations/ethical review; rigor and reproducibility; culture of care; occupational health/biosafety; and a greater exploration of behavioral management that incorporates housing, husbandry, and handling. Additional workshops may be convened to explore some of these issues more deeply, she said.

Speakers shared many references and suggestions for consideration in the *Guide* update, which are summarized in Resource Documents 2 and 3.

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