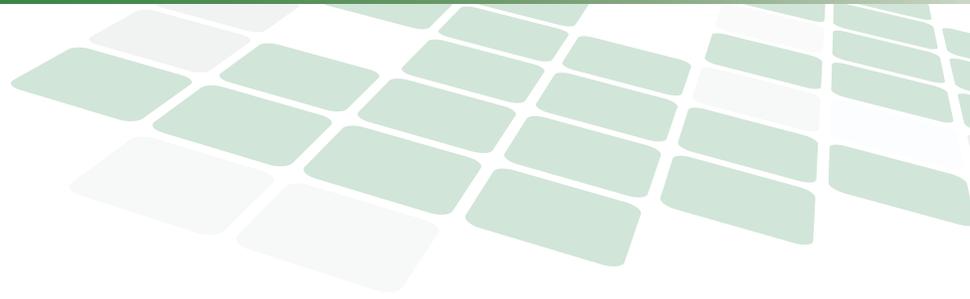


White Paper:

Your NIH Funding at Risk: New OLAW Guide Sets a High Bar for Cage Sizes



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Founder: Leslie C. Norins, MD, PhD

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If you don't comply with the NIH's new minimum standards for lab animal care and use, you could lose your grant funding. That's the big shake-up from the recently-released 8th Edition of the Guide for the Care and Use of Laboratory Animals.

The NIH's seemingly harmless recommendations for minimum cage spaces in particular have the scientific research world in an uproar -- and for good reason. The cage-space requirements are far larger than the current standard in most labs, and up until now you've had full latitude on deciding the floor space necessary for your lab mice and rats.

The NIH received an astounding 806 comments on the 8th Edition after the initial proposal. Comments poured in from individuals, institutions, professional organizations and even animal advocacy organizations. Hundreds more position statements and letters to NIH came to the forefront in response to the proposed Guide changes.

From these comments, OLAW's Position Statements outline and address the major points of contention in the Guide:

- 70 percent of respondents are concerned about the costs of complying with the Guide;
- 60 percent of respondents are concerned with the caging and housing changes in the Guide;
- 40 percent are concerned with the requirements for the research use of non-pharmaceutical-grade chemicals and substances;
- 30 percent are concerned about the requirements for food and fluid restriction; and
- 30 percent are concerned about the limit on the number of survival surgeries performed on each animal.

Beware of These Significant Animal-Housing Changes

OLAW expects you to base your animal care and use program on the 8th Edition effective Jan. 1, 2012. On page 57 of the Guide, you'll find Table 3.2, which outlines OLAW's recommendations on minimum cage space for lab rodents housed in groups.

Mice: Mice housed in groups should have a cage height of no less than 5 inches (12.7 cm) and a floor area per mouse of 6 to 15 inches (38.7 to 96.7 cm) squared, depending on body weight. A female mouse and her litter should have 51 square inches (330 cm) of floor space at a minimum.

Rats: All rats should have a minimum cage height of 7 inches (17.8 cm), according to the Guide. Rats housed in groups should have at least 17 to 70 square inches (109.6 to 451.5 cm) of floor space per rat, depending on weight. A female rat and her litter would need at least 124 square inches (800 cm) of floor space.

Hamsters: If you work with hamsters in your lab, you'll need a minimum of 10 to 19 square inches (64.5 to 122.5 cm) of floor space per animal and at least 6 inches (15.2 cm) in cage height. Guinea pigs need 60 to 101 square inches (387.0 to 651.5 cm) of floor space per animal with at least 7 inches (17.8 cm) of cage height.

According to the Guide, other factors that may increase or decrease these cage space figures include:

- Animals housed singly or in small groups may need more floor space than the recommendations;
- The dimension figures increase if you have various breeding configurations with multiple adults, multiple litters or litters with varying sizes and ages;
- Juvenile rodents typically require a larger cage space than adults, due to their higher activity level;
- Juvenile rodents may also require larger cage spaces than indicated by their size or weight, in anticipation of their full growth and adult size; and
- Larger groups can thrive in slightly higher-density housing, but not below the minimum recommended dimensions.

Rabbits: Rabbits should have a cage height of 16 inches (40.5 cm) and a floor space of 1.5 to 5.0 square feet (0.14 to 0.46 m) per animal, depending on weight, according to the Guide. In the position statements, OLAW reasserts that this cage height figure is a performance standard, and that "IACUCs may consider the use of a rabbit cage that is 14 inches in height, if appropriate."

Where Did NIH Get These Numbers?

If these figures seem a bit higher than your current cage dimensions, you're not alone. Not only are many

organizations balking at these cage size recommendations, but they're also questioning the basis for the specific numbers.

In the Guide, OLAW asserts that the minimum cage dimensions in Tables 3.2 (rodents), 3.3 (rabbits, cats and dogs), 3.4 (avian species), 3.5 (nonhuman primates) and 3.6 (agricultural animals) are based on "professional judgment and experience."

In a May 2011 letter to the NIH, the American College of Laboratory Animal Medicine (ACLAM) expresses its disapproval of the 8th Edition's cage size recommendations. "ACLAM is concerned that the new recommendations for specific rodent housing are not supported by the scientific literature, will have little-to-no measurable benefit on animal welfare, and yet will have a significant financial impact on animal care and use programs," the letter states. "These costs will be passed on to the investigators or will otherwise negatively impact research output."

Further, ACLAM points out that the NIH's recommendations seem to mirror mandates from the Annex II of the European Directive, but "the significant body of science supporting current breeding densities and paradigms in the U.S." don't fall inline with these cage size requirements.

Throughout the Guide, however, OLAW cites numerous studies on how various cage sizes relate to health, behavior, growth and other factors. But many respondents contend that a wide array of published research refutes these measurements and instead supports the use of smaller cage dimensions for lab rodents.

Adhere or Lose Your NIH Funding -- Or Not?

Much of the buzz surrounding the key changes in the Guide's 8th Edition revolves around just how serious the agency is about complying with the minimum cage space recommendations. Like many other groups, the American Aging Association (AGE) criticizes the 8th Edition's ambiguity in what recommendations are mandatory rules versus guidance.

A position statement by the American Physiological Society provides some cautionary advice for investigators who are reading the 8th Edition as recommendations only. "Since OLAW considers the Guide's technical standards 'federally enforceable,'" you need to "interpret 'must' and 'should' statements in the Guide as regulations rather than guidelines," the Society states.

Further, the Society points out that the 8th Edition is twice as long as the 7th Edition and includes significantly more “must” and “should” statements. “NIH has said it wants to reduce regulatory burden, but this Guide will increase burden on PHS funded institutions,” the Society criticizes.

Pay Attention to the Language: Performance Standards Vs. Practice Standards

The answer to whether your lab is at risk for losing NIH funding is all in the Guide’s language. Some standards and recommendations in the Guide are much more flexible than others.

Key: Throughout the Guide, pay attention to the “must” and “should” statements. OLAW is refining its “practice standards” and “performance standards.” Any “should” statements refer to the performance standards, which are the ideal. This means that you have some flexibility and discretion for achieving these standards.

“Must” statements are meant as practice standards, which are mandatory. “These standards, developed within the research community itself, reflect efforts to improve vertebrate animal welfare through self-monitoring and the application of outcome-based performance standards in striving for better animal care and use that benefits scientific research,” OLAW states.

In the Guide, you’ll notice that all of the significant additions or changes incorporate “should” statements and references to performance standards. This means that the NIH won’t necessarily yank your funding immediately if your lab animal practices aren’t exactly inline with the recommendations set out in the 8th Edition.

“Rodent cages of the size commonly used in the United States may be appropriate for trio breeding,” an OLAW official tells PIA. In fact, you should use the “performance standards approach” to complying with the Guide’s recommendations for your housing practices. “The 8th Edition of the Guide does not add specific, additional engineering standards for breeding configurations. This empowers institutions to determine appropriate housing,” the official explains.

Take action: So in light of these changes, what are your options for achieving these performance standards? You have three basic choices: 1) purchase larger cages that comply with the minimum space requirements set out in the Guide; 2) place fewer animals into each cage so that you’re in compliance; or 3) justify your current rodent housing arrangements to the IACUC.

What You'll Need to Prove

Your IACUC can permit exceptions to the Guide's rules, but only after individual review and approval. The IACUC's approval "must be based on scientific, veterinary medical or animal welfare issues," OLAW states in a recent public response to concerns over the Guide's changes. "Cost saving or convenience alone is not sufficient justification to approve a departure from the minimum standards of the Guide."

An OLAW official tells PIA that the IACUC must consider relevant factors when assessing your cage space, based on the performance standards. Factors might include:

- The rodent strain's average litter sizes;
- Whether you have multiple litters in a single cage;
- The different ages of the pups in the different litters;
- The pups' growth rates;
- The need for cross-fostering;
- The current cage dimensions; and
- Your overall management and husbandry practices, such as bedding changes and cage sanitation.

"Cages that might be acceptable when litters are born may have insufficient space as pups grow," the official warns. Whatever parameters you use to establish breeding configurations and weaning procedures, "the IACUC must ensure that cage population does not negatively impact animal well-being and overcrowding does not occur."

The following additional factors will affect the IACUC's review of rodent cage sizes:

- The animals' ages, body weights and sexes;
- The number of animals in cohousing arrangements versus singular housing;
- The duration of accommodation;
- The animals' intended use (breeding/production vs. experimentation);
- Cage volume and spatial arrangement;
- Sufficient space allowance for postural expression and other species-specific behaviors;
- Clearance for cage structures like feeders, water containers, enrichment devices and litter boxes (not included in floor space measurements);

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- All performance indices: health, reproduction, growth, behavior, activity and use of space; and
 - All special needs: obese, hyperactive and arboreal animals.

For rabbits, IACUCs should review and approve cage heights less than 16 inches based on whether the cage:

- Preserves animal well-being;
- Provides sufficient space to meet the rabbit's physical, physiologic and behavioral needs;
- Allows the rabbit to hold its ears in an upright position, without forcing it to fold over its ears by contact with the cage ceiling; and
- Other factors based on performance indices and special needs determined by the rabbit breed's characteristics.

What to Change Regarding Non-Pharmaceutical-Grade Substances

The AGE expresses additional concerns in a letter to the NIH: "The Guide mandates the use of commercially-produced, pharmaceutical grade compounds in animals whenever possible, with active justification and additional approval needed via the local IACUC whenever such chemicals are not used."

According to the 8th Edition, when you're using non-pharmaceutical-grade chemicals/substances, you must seek approval from your IACUC. The IACUC will base its approval upon the substance's:

- Purity;
- Grade;
- Sterility;
- Acid-base balance;
- Stability;
- Pyrogenicity;
- Osmolality;
- Site and route of administration;
- Compatibility of components;
- Adverse reactions and side effects;
- Pharmacokinetics; and
- Storage.

OLAW gives the IACUC full latitude on how to review and approve the use of non-pharmaceutical-grade agents. The IACUC “may establish acceptable scientific criteria within the institution, rather than on a case-by-case basis,” OLAW states. The same evaluation factors apply to non-survival studies as well.

Heed Changes to Food/Fluid Restriction

OLAW changed the Guide’s recommendations regarding food and fluid restriction and the use of preferred foods, but the IACUC may or may not force you to adhere to these guidelines. The IACUC will evaluate your methods based upon:

- The level of restriction and potential adverse consequences in regulating food or fluid;
- How you assess the health and well-being of the animals involved in food/fluid regulation activities;
- Adequate maintenance of hydration, body weight, and behavioral and clinical health; and
- Whether the animal is receiving its minimum daily requirements of food and fluid.

Another change in the Guide that’s under fire is multiple surgical procedures on a single animal. OLAW is allowing the IACUC to determine the impact of multiple procedures on an animal’s well-being, but the Guide states that multiple major surgical procedures on a single animal are acceptable only if they’re:

- Necessary for clinical reasons;
- Included in and essential components of a single research project/proposal; or
- Scientifically justified.

Put simply, you must prove to the IACUC that performing multiple procedures on a single animal is crucial to your research despite the effects on the animal’s well-being.

The Bottom Line

The most important factors to keep in mind as you’re perusing the 8th Edition of the Guide is to look for the “must” (practice standard) and “should” (performance standard) statements. Picking out this language will help you to understand what changes will and will not immediately threaten your NIH grant funding.

Either way, the changes in the Guide will likely place you into ongoing communication and collaboration with the IACUC, as you work toward figuring out what you need to change and what you can justify to keep status-quo. Start working with your IACUC now to stay in compliance. ■

Resources

View the Guide at:

<http://grants.nih.gov/grants/olaw/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf>

View the related NIH notice NOT-OD-12-020 at:

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-020.html>

View OLAW's Position Statements on the Guide at:

<http://grants.nih.gov/grants/olaw/2011positionstatement.htm> ■

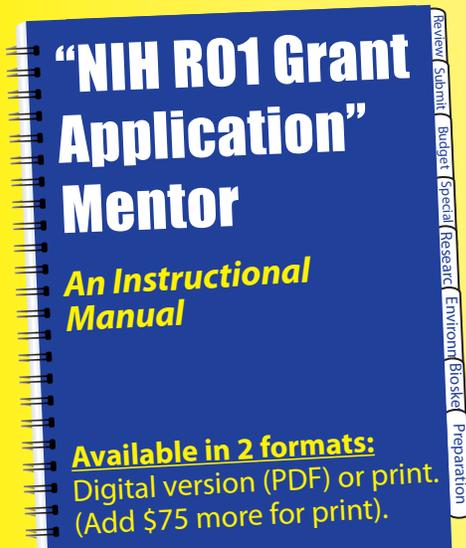
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