

The American Aging Association Position on adopting the 8th Edition of the *Guide for Care and Use of Laboratory Animals*

BACKGROUND:

The previous edition of the Guide, implemented in 1996, (NOT-OD-06-011) sets forth standards for humane animal research as we have known it over the last 15 years. The guide specifies details of infrastructure, construction, and operation of animal facilities, including the issues of rodent density per cage, rodent breeding and many other critical issues. These specifications are treated not merely as guides, but rather as federal rules. There is clear indication that the same will be the case with the new version of the Guide, should it be adopted.

The new version of the Guide contains improvements in standards in laboratory animal programs that are meritorious and that would improve animal welfare. However, the concern the scientific community has over the new Guide is at least threefold:

1. One major concern is treatment of the Guide as a set of de facto mandatory rules, rather than a guide; particularly in cases where such rules have not been properly justified, as is the case with the animal facility building standards.
2. There are several key specific issues where the Guide does NOT make improvements but rather makes changes either without scientific evidence or contrary to scientific evidence related to animal welfare.
3. Finally, 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.

The points above are discussed more detail below:

1. The following is an informative passage from the statement of the American Physiological Society relative to the mandatory, rather than the guiding, nature of the Guide:

“Since OLAW considers the *Guide*’s technical standards “federally enforceable” (Wolff, *Lab Animal*,10:40, 2007), PHS-assured programs have to interpret “must” and “should” statements in the *Guide* as regulations rather than guidelines. OLAW’s FAQ F10 states that it “expects institutions to use the *Guide*’s engineering standards as a baseline.” FAQ F10 permits exceptions to be considered by the IACUC, but each must be reviewed individually. NIH has said it wants to reduce regulatory burden, but this *Guide* will increase burden on PHS funded institutions. The document has been doubled in length and includes significantly more “must” and “should” statements than the 7th edition. This increasingly directive approach reflects specified engineering standards and undermines the flexibility that previously permitted institutions’ animal care teams to select the best way to achieve desired outcomes.

The *Guide* became a regulatory document when the Health Research Extension Act made compliance with the PHS Policy on Humane Care and Use of Laboratory Animals a legal requirement for NIH grants involving vertebrate animals. Since the PHS Policy requires institutions to use the *Guide* “as a basis for developing and implementing an institutional

program for activities involving animals” (PHS IV.A.1), changes to this document should be subject to regulatory notice and comment requirements.”

2. The second issue is the lack of scientific evidence in mandating changes in animal welfare. This encompasses parts of the 7th edition of the *Guide*, which were adopted unchanged and which were not justified before, as well as the guidelines about rodent density in the new edition, which are adopted contrary to the scientific evidence.

Again, the APS provides the following extensive rationale and the background for this: “A brief review of the literature identifies four main issues casting doubt on the scientific support for specific rodent cage density recommendations in Table 3.2.

1) Rodent cage density recommendations in the *Guide* are not accompanied by supporting scientific data. To the contrary, studies over the past decade have demonstrated that animal health and well being can be maintained at higher cage densities than those recommended in the 7th edition of the *Guide*, which similarly lacked supporting data. (See Gonder and Laber *ILAR J* 2007: 48:29; McGlone, et al, *Contemp Top Lab Animal Sci*: 2001: 40:21; Smith, et al, *Comp Med* 2004: 54:656; Smith, et al, *Comp Med* 2005: 55(4) 368-76).

Research in some strains of mice demonstrates improved health in mice housed at higher compared to lower densities and also suggests that cross-fostering (e.g., in trio breeding settings) can improve the health of neonatal mice (Smith and Corrow (*ILAR J* 2005: 46(2) 140-7).

2) The new *Guide* adds “female + litter” cage area recommendations for mice and rats without supporting citations. In fact, the literature provides some evidence that cage size has no impact on litter size, litter survival, body weight of the pups or long term behavioral effects (Whitaker, et al, *Lab Animal* 2007: 36:32).

3) Various parameters have been studied to assess optimal cage density, including litter size; pup and dam body weight; litter survival; environmental conditions of the cage such as ammonia; behavior indices of the offspring such as aggression, preference tests, stereotypies; and physiological variables such as stress indices, immune function, cardiovascular parameters, and bone density. However, to date there is no scientific consensus on what provides the best measure(s) of animal welfare.

4) Evidence also suggests that the strain of the rodent may influence outcomes, which argues against uniform requirements by species. The APS recognizes that the *Guide* committee intended that its recommendations would be implemented as performance standards. However, OLAW has indicated both in FAQ F10 and elsewhere that the *Guide*'s technical standards will function as engineering standards. This approach will be deleterious to the strains that do better with higher cage density.

Thus, our initial survey of published findings shows that further review of the literature is needed to determine whether scientific evidence supports the rodent cage density recommendations of the new *Guide*.”

3. The new section “Use of Non-Pharmaceutical Grade Chemicals and Other Substances” would require researchers to abandon use of standard source chemicals in pharmacology (and biogerontology) research in favor of costly pharmaceutical grade human or veterinary preparations, when available, “to ensure that toxic or unwanted side effects are not introduced into studies conducted with experimental animals.” The use of NP grade chemicals can be justified under the new guidelines, when pharmaceutical grade compounds or substances are unavailable and justified by research subject to approval of the local IACUC, in which consideration should be given

to the grade, purity, sterility, pH, pyrogenicity, osmolality, stability, site and route of administration, formulation, compatibility, and pharmacokinetics of the chemical or substance. While in principle this policy is consistent with animal welfare and good research practice, it is the view of the American Society for Experimental Therapeutics (ASPET) and College on Problems of Drug Dependence (CPDD) that use of NP grade chemicals from standard source vendors is not a significant threat to animal welfare, whereas pharmaceutical grade preparations are problematic and introduce confounding in most scientific applications. Problems with pharmaceutical grade preparations are detailed in the statement from ASPET attached. It is important to note that this guideline discourages use of chemicals/substances from reliable private vendors and chemists, including those working directly in NIH intramural programs and suppliers/submitters to NIH-sponsored programs such as the NIA Interventions Testing program and the NIDA drug supply program.

The definition of “pharmaceutical grade” is not clear from the *Guide* as written, which constitutes an additional concern and adds an element of uncertainty as to how this guideline should be interpreted. The following is paraphrased from the CPDD statement posted in the Federal Register:

No definition of “pharmaceutical grade” is given, but two conflicting definitions are implied by citation of the USDA/APHIS Policy 3: (i) an interpretive rule for use of “medications” to prevent pain/distress and (ii) the intramural NIH program policy on “non-pharmaceutical grade drugs.” Experience with USDA/APHIS enforcement makes clear that Policy 3 is interpreted as requiring use of commercially prepared solutions, rather than investigator-prepared, and the first sentence of the new Guide section on this topic is consistent with this. Yet the intramural policy defines “pharmaceutical grade” as manufactured according to USP standards, thus accommodating investigator-prepared solutions. Even the intramural Policy ignores that NIH-sponsored and other standard sources do not prepare to USP standards, as these have more to do with documenting drug manufacture than drug quality. As with other sections, the contradictions in guidance are problematic. Reconciling definitions is one obstacle to interpretation, but the clear requirement that investigators justify the use of certain types of compounds and provide elaborate detail on their preparation and characteristics for IACUC review is only one example of the new Guide’s intrusion into the realm of the scientific and professional judgment of NIH-funded researchers.

Additional links and resources:

1. Full 8th Guide document: The Guide is available to download<

<http://click.icptrack.com/icp/relay.php?r=15987573&msgid=327731&act=2LGN&c=248297&destination=http%3A%2F%2Fgrants.nih.gov%2Fgrants%2Folaw%2FGuide-for-the-Care-and-Use-of-Laboratory-Animals.pdf>> and may be viewed or purchased from the National Academies

Press<http://click.icptrack.com/icp/relay.php?r=15987573&msgid=327731&act=2LGN&c=248297&destination=http%3A%2F%2Fwww.nap.edu%2Fcatalog.php%3Frecord_id%3D12910>.

APS, AAI and ASPET comments can be found at : <http://www.the-aps.org/pa/>;
http://grants.nih.gov/grants/olaw/rfi_lab_animal_standards/RFI-Report.pdf; and
<http://www.aspet.org/Blog.aspx?id=2101&blogid=219>, respectively.

2. NABR comment draft : (from the NABR site) :

To assist with the preparation of your comments, NABR has drafted a comment letter<http://click.icptrack.com/icp/relay.php?r=15987573&msgid=327731&act=2LGN&c=248297&destination=http%3A%2F%2Fwww.nabr.org%2FNABR_Draft_Comments_On_Guide_MSWord.aspx> which will be submitted on behalf of the membership. Please feel free to endorse, use language from and/or add information based on your situation and concerns.

POSITION – POSTED COMMENT:

On May 23, on behalf of the American Aging Association, Dr Janko Nikolich-Zugich, Immediate Past President, had posted the following comment at the NIH OLAW (Office of Laboratory Animal Welfare) comment site <http://grants.nih.gov/grants/olaw/2011guidecomments/add.htm> in response to the two questions for which the comments were requested:

1. **Should NIH Implement the 8th edition of the *Guide for the Care and Use of Laboratory Animals*?**

The American Aging Association (AGE) is an organization with over 200 members performing cutting-edge experimental research in biogerontology, and encompassing a broad range of specific interests in the aging of different cells, tissues, organs and organisms, with the mission to understand the aging process and improve quality of life of older adults. AGE joins the NABR, and the many scientific societies, including the FASEB member societies, in urging the NIH **not to adopt the new *Guide without further discussion and modification***. We will not reiterate the comprehensive and eloquent comments made by the other associations, chiefly the NABR, but will simply stress three urgent points requiring modification:

- a. Flexibility related to the performance of animal facilities: OLAW should explicitly clarify that the Guide can be used as a guidance document with a primary emphasis on performance and NOT a prescription of mandatory engineering standards. Otherwise, the new *Guide* should be subject to extensive review and comment.
- b. Proposed changes in rodent housing density: evidence was not presented to document that changes proposed in the new *Guide* are needed to ensure animal welfare. Therefore, such changes should be postponed and also thoroughly reviewed before any implementation. Given that NABR data demonstrate significant impact upon the practices and costs of rodent breeding of the proposed cage size increase, this change is likely to erode the already shrinking ability of the NIH to support science. It is therefore imperative that we scientifically document the benefit of this change for animal welfare, by evaluating whether the current practices of the 7th Guide may be faulty or insufficient, and, if they are, would the recommended changes in the 8th *Guide* be most appropriate to correct such shortcomings. An additional concern is that artificially reducing social interactions between rodents may lead to neuropsychological changes that could affect various processes, including the process of aging, making the results of the new studies poorly compatible with prior studies performed under different housing densities.
- c. Favoring the use of commercially- prepared “pharmaceutical grade” chemicals: AGE joins the sentiments of the ASPET that commercial preparations are not

designed for experimental testing but instead introduce confounding variables. The increased regulatory burden instituted for the use of non-pharmaceutical grade compounds would represent a serious impediment to progress in research without discernible benefit to animal welfare. The guidelines pertaining to “Use of Non-Pharmaceutical-Grade Chemicals and Other Substances” needs to be thoroughly re-evaluated and revised.

2. Should NIH implement the 8th edition of the Guide as proposed in NOT-OD-11-042?

The American Aging Association advises against any implementation of the current version of the 8th edition of the Guide in its current form. Should the Guide be adequately revised, as commented under #1 above, the NIH should then reconsider the timetable in light of the revisions. At that time, the NIH would be wise to take into account the realistic implementation of the provisions of the Guide that relate to facilities and their inspections. In doing so, any disruption of the ongoing, and particularly longitudinal, animal experiments should be avoided and care should be taken to avoid inadvertently harming animals and confounding the results of ongoing research.