

Earthquake!

Great Eastern University (GEU)'s research portfolio includes considerable animal use activities that primarily involve mice and rats. GEU's Attending Veterinarian, Tracy Thompson, recognized that the number of researchers at GEU was increasing and that, based on the ongoing trend, vivarium space would be at capacity in less than a year. Thompson broached the space concern with the Institutional Official (IO), explaining that GEU needed to expand the vivarium by the end of the year or GEU's ability to accommodate new research activities would be limited. The IO agreed to fiscally support adding new housing space adjacent to GEU's largest vivarium, which was already at its maximum capacity.

Construction started immediately. Although the new space was not structurally affecting the current vivarium, the construction resulted in excessive noise and vibration within the existing vivarium space. Researchers immediately expressed concern to Thompson; they noticed behavioral changes in their animals and decreased numbers of offspring being produced in critical strains. Thompson explained that the physical plant directors assured her there would be no impact on the current vivarium and, that unfortunately, the circumstances prevented the relocation of animals since there simply was not available space. The veterinary staff agreed to increase animal "well-visits" to ensure ongoing observation of the affected animals.

Dr. Samantha Gedrag is a behavioral scientist who performs various behavioral studies that involve both *Mus Musculus* and two strains of *Peromyscus*. A month into the construction process, Dr Gedrag submitted a protocol modification requesting for 1,000 more mice, and justifying the increase in mice by the environmental changes introduced by the construction. She explained that the data collected during the construction period was significantly skewed and unusable due to the vibrations. Consequently, the lost animals would have to be replaced for her to complete the objectives of her NIH grant. Furthermore, she thought it was necessary to place her project on hold until the construction was complete, and the remaining animals were reaccimated. An IACUC member asked that the protocol amendment be reviewed via full committee review and that Gedrag participate in the IACUC meeting and discussion.

During the IACUC meeting, Gedrag explained that her research includes multiple behavioral tests that had been repeated for over two years. Prior to construction, she conveyed the mentioned welfare concerns to Thompson and was assured the construction activities would have no impact on her animals. It soon became evident that the research data collected during the construction period was significantly different from that collected for the past two years, and that the construction activities were the only new research variables. Gedrag was concerned, in her opinion, with the waste of animal, the extreme financial burden placed on herself and the lab, and whether her NIH funds could be used to support the activities performed during the construction period. Consequently, in addition to approving her request to increase her animal numbers, Gedrag was expecting the IACUC to support her proposal to have the institution reimburse her for the lost fiscal resources that she incurred during the construction period. She left the room and the IACUC began its deliberation; how should the IACUC address the following concerns?

- Should the IACUC approve the request to increase the animal numbers based on the provided justification?
- Is the IACUC in a position to support her request to have all the associated expenditures reimbursed?

A WORD FROM OLAW

In this scenario, because of noise and vibration from construction adjacent to the vivarium, animals are exhibiting behavioral changes and reduced fecundity impacting ongoing research. The resulting environment does not meet the requirements of the PHS Policy for proper living conditions or the expectations of the *Guide* for facilities to minimize unnecessary noise and vibration¹⁻³. The IACUC, the institution, and the Principal Investigator (PI) must each address the problem. Key functions of the IACUC are to review concerns involving the care of animals, make recommendations to the Institutional Official (IO), and, through the IO, provide OLAW an explanation of the circumstances of any serious or continuing noncompliance with the Policy or serious deviation from the *Guide*¹. To address the unusable data and need for additional animals to complete the study, the IACUC should allow changes to the approved activity, which should resume only when the living conditions comply with the PHS Policy and the *Guide*'s expectations. The IACUC should also promptly inform the IO of the situation, that reporting to OLAW is indicated and the institution should consider compensation for the lost efforts. The IO, by signing the institution's Assurance with OLAW, must have the authority to commit institutional resources to meet the requirements of the Policy^{1,2,4}. The PI is required by the NIH Grants Policy Statement to report annually in the Research Performance Progress Report (RPPR) to the NIH

funding component. In the RPPR, the PI must report any challenges or delays in the project with plans for resolving them, and significant changes regarding animal subjects^{5,6}. The PI may also contact the NIH Program Official who monitors the grant to discuss the research interruption and its potential impact on the grant⁷. □

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References

1. Public Health Service. *PHS Policy on Humane Care and Use of Laboratory Animals*. (US Department of Health and Human Services, National Institutes of Health, Bethesda, MD, 2015).
2. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals*. 8th edition, p 50, (National Academies Press, Washington, D.C., USA, 2011).
3. Brown, P. *Lab Anim (NY)* **49**, 270 (2020).
4. Public Health Service Policy on Humane Care and Use of Laboratory Animals – Frequently Asked Questions. Institutional Responsibilities, Question No. G.5. *What is the difference between the Institutional Official and the Chief Executive Officer?* (US Department of Health and Human Services, Bethesda, MD, USA). <https://olaw.nih.gov/faqs#/guidance/faqs?anchor=50380>
5. National Institutes of Health. NIH Grants Policy Statement, 8.4.1.1 Non-Competing Continuation Progress Reports. (US Department of Health and Human Services, Bethesda, MD, USA). https://grants.nih.gov/policy/nihgps/HTML5/section_8/8.4.1_reporting.htm#Non-Comp
6. National Institutes of Health. Grants & Funding, About Grants, *Research Performance Progress Report (RPPR)*. (US Department of Health and Human Services, Bethesda, MD, USA). <https://grants.nih.gov/grants/rppr/index.htm>
7. National Institutes of Health. Grants & Funding, Need Help? *Understand Staff Roles, Program Officials*. (US Department of Health and Human Services, Bethesda, MD, USA). <https://grants.nih.gov/help/ic-staff-roles#program-official>

- Should the issue be reported to OLAW and NIH Grant's Management as a non-compliance or a programmatic concern? □

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How Much Stress Is Too Much?

The researchers in this example are rightfully concerned by the impact of an obvious source of stress such as excessive noise and vibration on the outcome of experiments, particularly those that need to be compared with studies done prior to

COMPLIANCE CONSIDERATION

The Protocol Review coordinators offer the following compliance considerations:

1. What do the regulation(s) say about noise levels?

The *Guide* specifically emphasizes the need to manage “Noise and Vibration”¹. It does focus on the fact that IACUCs should ensure daily operations such as equipment, cage changing, facility design (e.g., neighboring species, HVAC) do not create environmental conditions that could negatively impact animals. Although not directly related to the normal observations of a vivarium, Dr. Gedrag's concern still involves a type of noise and vibration that was anticipated as a result of the construction. The *Guide's* section on noise and vibration control² speaks to the importance of positioning animal rooms away from sources of noise and vibration.

OLAW has previously indicated³ that “the PHS Policy requires that the living conditions of animals contribute to their health, and the *Guide* expects facilities to minimize the production of unnecessary noise and vibration” and that any harm caused to animals as a result of construction-related noise and/or vibration is “a programmatic failure”. Accordingly, the issue must be reported to OLAW and NIH as a non-compliance and/or a programmatic concern.

2. Should the IACUC approve the request to increase the animal numbers based on the provided justification?

It is the responsibility of each institution to use the minimum number of animals required to satisfy the research goals. The IACUC should consider that the proposed research goals cannot be achieved since a high percent of the animals have not produced

the construction. Naturally, we all want our baseline in control groups to be the same across experiments, as we test and compare variables in our experimental groups. But, in our view, the situation described here is just one aspect of a larger problem which is slowly

usable data. Consequently, continuing the research without an adequate number of animals could result in the generation of additional incomplete data and the waste of animal resources. As a result, Dr. Gedrag may not be asking to increase the number of animals she previously estimated as being needed to obtain valid results, but rather asking to replace the animals that could not be used because of the negative impact of the noise and vibration from the construction.

3. Is the IACUC in a position to support her request to have all the associated expenditures reimbursed?

One of the IACUC's functions (per federal mandate) is to “make recommendations to the Institutional Official (IO) regarding any aspect of the institution's animal program, facilities, or personnel training”⁴. Accordingly, it is within the IACUC's jurisdiction to support Dr. Gedrag's request for institutional financial support; however the IACUC's authority extends only to a recommendation to the IO. □

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References

- Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals*. 8th edn., 49-50. (National Academies Press, Washington DC, 2011).
- Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals*. 8th edn., 142. National Academies Press, Washington DC, 2011.
- Brown, P. *Lab Anim (NY)* **49**, 269 (2020).
- Public Health Service. *PHS Policy on Humane Care and Use of Laboratory Animals*. (U.S. Department of Health and Human Services, National Institutes of Health, Bethesda, MD, 2015). pgs 12-13

gaining attention. Specifically, there are other “not so obvious” sources of significant chronic stress that are now recognized to be skewing the outcome of experiments. A growing literature supports the conclusion that subtle, housing-related parameters imposed upon mice are causing a variety of metabolic and immunologic changes that have the potential to alter the outcome of multiple murine models of human disease. For example, the mildly cool temperatures at which mice are housed is one important example of stress-inducing parameter that is already undermining the interpretation of data¹⁻⁴. One of these effects is significant suppression of immune responses⁵, which can for example skew the apparent effectiveness of immunotherapies or affect neural activity.

At the most recent meeting of AALAS, an entire Symposium session was devoted to the matter of mouse husbandry, especially subthermoneutral housing, and its relationships to stress (AALAS, KY, 2022 “Rodent Thermoregulations at the Housing Level, Why Does it Matter?”). Until we can assess the relative effects of different stressors associated with baseline mouse husbandry on experimental outcomes, the scenario outlined here is just a matter of adding one more stress!

How much stress is too much? The questions posed here are likely to be raised at multiple Institutes, as researchers become more aware of the substantial impact of standard housing guidelines on the outcomes of their experiments. For example, Lewejohann et al., discuss the importance of designing experiments with the Experimental Design Assistant (EDA) to consider the sources of bias at the design stages of the experiment, before the data are collected⁶. Similarly, transparent reporting of research methods and findings (that include variables of housing conditions) is an essential component of reproducibility⁷. It is very worthwhile in our view for additional discussion with granting agencies, IACUC and researchers to determine what level of stress is sufficient for skewing the outcome of experiments. We predict that it is much lower than the excessive noise and vibration imposed in this scenario.

Should the IACUC approve the request to increase the animal numbers based on the provided justification?

Yes, as long as Dr. Gebrag waits to initiate her study until after the construction is completed.

Is the IACUC in a position to support her request to have all the associated expenditures reimbursed?

After initial review of the complaint the IACUC should determine whether it requires a) further investigation and immediate action, b) further investigation but no immediate action or c) no action. In this case, the IACUC will probably need to have further investigation and no immediate action since neither animal nor human health is compromised. The vibration and noise from the construction has obviously affected how the animals responded to the study, but they are not in danger. If the construction did in fact affect Dr. Gebrag's data, the IACUC can support her request for reimbursement since she would have to repeat her study.

Undoubtedly there is a psychological effect from the bouts of construction that have influenced the behavior of the mice. This raises the need for renewed attention to the role of stress in general in research colonies. This is critical since, as mentioned above, there are other sources of stress imposed by standard housing. Guidelines are therefore needed to determine what Institutes should be reimbursing for experiments that are being skewed by different degrees of stress.

Should the issue be reported to OLAW and NIH as a non-compliance or a programmatic concern?

Since the research activities were not suspended by IACUC but the researcher herself due to an adverse event, it will not be reported by IACUC; but the researcher should report the delay to the granting agency, in this case the NIH. Ultimately, the role of stressful environmental conditions to cause skewing of research data is an

important matter that needs to be recognized and addressed by all stakeholders. □

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References

- Hylander, B. L., Repasky, E. A. & Sexton, S. *Animals (Basel)* **12**, 371 (2022).
- James, C. M., Olejniczak, S. H. & Repasky, E. A. *Temperature* <https://doi.org/10.1080/23328940.2022.2093561> (2022).
- Hylander, B. L., Gordon, C. J. & Repasky, E. A. *J. Immunol.* **202**, 631–636 (2019).
- Seeley, R. J. & MacDougald, O. A. *Nat. Metab.* **3**, 443–445 (2021).
- Mohammadpour, H. et al. *J. Clin. Invest.* **129**, 5537–5552 (2019).
- Lewejohann, L., Schwabe, K., Häger, C. & Jirkof, P. *Lab. Anim.* **54**, 150–158 (2020).
- Percie du Sert, N. et al. *PLoS Biol.* **18**, e3000410 (2020).



Motion Causes Research Commotion On Animals and PIs

As research programs expand, renovation of current facilities and construction of new facilities is inevitable to meet the demand for vivarium and procedural space. No matter how well programs plan or prepare for the construction, vibration and noise are difficult factors to predict.

Per the *Guide*¹, “facilities should minimize the generation of vibration, including from humans, and excessive vibration should be avoided.” Generation of vibration may be unavoidable during renovation or construction, but there are mitigation techniques that could be employed to reduce the impact on animals and research outcomes. Sensitive animals may need to be moved to facilities away from construction zones, or vibration suppression systems can be implemented to reduce the impact. Principal Investigators (PIs) should be notified of the construction plans and timelines, and of the possible effects that it may have on the animals.

Great Eastern University (GEU) failed their researchers by not discussing construction plans with them prior to initiation of work. Researchers may have been able to alter timelines and testing due to the noise/vibration. GEU also failed to take the researchers initial concerns and complaints seriously after construction started and only instituting

additional “well animal” observations when behavioral changes and decreased numbers of offspring were reported. The architects and plant directors were incorrect that a construction built adjacent to existing vivarium space would have no impact on the vivarium or the animals. Dr. Gedrag was correct in her concerns prior to the construction and it is unfortunate that a vibration suppression system was not incorporated into the animal rooms to help minimize the impact.

Dr. Gedrag is fully justified in requesting additional animals to repeat the experiments, as it is well understood that noise and vibration have significant effects on behavioral studies. The *Guide*¹ (pg. 149) specifically discusses that the facility site used for behavioral studies “should be carefully selected to minimize airborne transmission of noise and groundborne transmission of vibration.” Amending the protocol to continue her research on a new cohort of animals would be appropriate after the construction has finished. However, it is beyond the IACUC's scope, based on the committees functions outlined in the Public Health Service Policy² and the *Guide*¹, to support her request to have the institution reimburse her for replacement animals or associated expenditures.

The increased and prolonged stress on the animals because of the construction

is a deviation from the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training*³. Principal VII states “The living conditions of animals should be appropriate for their species and contribute to their health and comfort...” The deviations from the Policy and the provisions outlined by the *Guide*¹ would require prompt reporting to OLAW as outlined in NOT-OD-05-034³ as well as to AAALAC if GEU is AAALAC-accredited. □

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References

- Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals*, 8th ed. (National Academies Press, Washington, DC, 2011).
- OLAW, NIH. *Public Health Service Policy on Humane Care and Use of Laboratory Animals*. (US Department of Health and Human Services, Bethesda, Maryland, USA, 2015). <http://olaw.nih.gov/policies-laws/phs-policy.htm>
- NIH. *Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals*. Notice NOT-OD0-05-034 [online]. (National Institutes of Health, Bethesda, MD, 24 February 2005). <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-034.html>