



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:

Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, Maryland 20892-6910
Home Page: <http://grants.nih.gov/grants/olaw/olaw.htm>

FOR EXPRESS MAIL:

Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 480-3387

May 31, 2022

Re: Animal Welfare Assurance
A3416-01 [OLAW Case 2K]

Pramod Khargonekar, Ph.D.
Vice Chancellor for Research
University of California-Irvine
(b)(4) Aldrich Hall
Irvine, CA 92697-3175

Dear Dr. Khargonekar,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your May 20, 2022, letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the University of California, Irvine. According to the information provided, OLAW understands that it was identified during a semiannual inspection that laboratory personnel failed to administer post-surgical analgesia to twelve rats, as approved in the protocol. Several factors apparently contributed to the unavailability of buprenorphine, including a recall of the laboratory's inventory, being out of stock at the laboratory's primary vendor, the replacement order using an alternate vendor getting misplaced in departmental processes and failure of laboratory personnel to follow-up on the order. However, laboratory personnel opted to proceed with performing the surgical procedures prior to securing appropriate analgesics. There were no animal welfare issues to report as a result of the PHS-supported noncompliant animal activity.

The corrective actions consisted of using a checklist, which includes administration of analgesics as a required step, that will be reviewed by senior laboratory personnel and subsequently reported to the Principal Investigator (PI). The weekly laboratory meeting agenda will include time dedicated to discussing IACUC protocol compliance items, and in the event any issues are identified, the PI and laboratory personnel will consult with the IACUC administrative office for guidance.

Based on its assessment of this explanation, OLAW understands that the University of California, Irvine implemented measures to correct and prevent recurrence of this problem. Your prompt and thorough resolution of this matter is commendable and consistent with the PHS Policy philosophy of monitored self-regulation. We appreciate having been informed of this matter and find no cause for further action by this Office.

Sincerely,

Neera V. Gopee - Digitally signed by Neera V.

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Gopee -S

Date: 2022.05.31 10:32:43 -04'00'

Neera V. Gopee, DVM, PhD, DACLAM, DABT
Associate Director, Animal Welfare Policy
Office of Laboratory Animal Welfare
National Institutes of Health

cc: IACUC Chair



Office of Research
160 Aldrich Hall
Irvine, CA 92697-7600

May 20, 2022

Brent Morse, DVM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, MD 28092

RE: University of California, Irvine – Animal Welfare Assurance number D16-00259 (A3416-01)

Dear Dr. Morse,

The University of California, Irvine (UCI) is reporting an incident of non-compliance on a federally funded study under an approved animal use protocol using rats. Funding for the project is provided by NIH grant number 1R21EB024793.

The protocol noncompliance was discovered during a semiannual IACUC facility inspection conducted on May 3, 2022. During the 5/3/22 inspection, laboratory personnel stated to the IACUC site visit team that due to an inability to obtain buprenorphine, rats that underwent survival surgeries were not provided with the analgesic. However, the approved protocol requires buprenorphine to be administered to animals at the end of surgeries and every 8-12 hours afterwards as needed. The site visit team emphasized the importance of administering analgesics to minimize pain in animals undergoing survival surgeries and reminded laboratory personnel that all procedures must be followed as described in the approved protocol. The problem was swiftly corrected the same day, buprenorphine from the university's Veterinary Services was provided to the lab and lab staff immediately administered the buprenorphine to animals that were supposed to have received it. The next day, the IACUC administrative office contacted the PI for more information as part of fact-finding efforts to understand the causes leading up to this serious error.

The PI was prompt in providing the IACUC with a well-detailed response along with the surgical and post-operative records of all animals affected by this situation. The response and records were reviewed and discussed by the full committee at its convened meeting on May 12, 2022, and the incident is as summarized:

- In April 2022, a total of 12 rats did not receive buprenorphine as required – nine rats underwent EEG electrode implantation surgeries, and three rats underwent practice sham surgeries.
- All 12 animals were closely monitored, and no signs of distress were noted.
- For the nine animals that underwent EEG electrode implantation surgeries:
 - As of 5/9/22, six were still alive and three were euthanized.
 - Of the three animals that were euthanized, one was euthanized and removed from the study due to dental malocclusion unrelated to the experiment, another was euthanized after reaching the experimental endpoint, and another was euthanized after developing aggression. The aggression in the one rat didn't occur until several weeks later, which seemed unrelated to the surgery or lack of buprenorphine.
- For the three animals that underwent practice sham surgeries, as of 5/9/22 one was still alive and two were euthanized after reaching experimental endpoint.

B. Morse, 5/20/22

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- Various factors contributed to the problem of buprenorphine becoming unavailable in the PI's lab: recall of the lab's inventory late last year, the lab's primary vendor being out of stock, the replacement order with an alternate vendor getting lost in department processes, and failure to follow-up by the PI's lab.
- Rather than suspend implantation surgeries, the PI's lab elected to proceed with the experiments before securing appropriate analgesics and unfortunately as a result, there were animals that didn't receive the proper analgesics as required.
- The PI's proposed plan to prevent recurrence includes multiple additional checkpoints and a more structured reporting hierarchy: 1) Adding a checklist to be used for all animals undergoing surgeries, which incorporates administration of analgesics as a required step, 2) Checklists will be reviewed by senior lab members and then reported to the PI, and 3) Devoting a specific IACUC protocol compliance agenda item to weekly lab meetings, to allow time for lab staff to discuss any issues that may arise. If issues are identified by the PI and lab staff, they will consult with the IACUC administrative office for guidance.

The committee agreed with the PI's proposed plan and recognized that their lab has had an excellent history of compliance and dedication to animal welfare for many years. The PI and their study team have been forthcoming with information and prompt in responding, expressing great remorse for this unfortunate but serious incident. The IACUC considers the PI's actions appropriate, and the matter resolved.

Please feel free to contact me or the IACUC Chair, Dr. Nancy Burley, if you have questions.

Sincerely,

DocuSigned by:
(b) (6)
785EBC7D29AB4F6...

Pramod Khargonekar, Ph.D.
Vice Chancellor for Research

cc: IACUC Chair N. Burley
Attending Veterinarian C. Lindsell (b) (6)

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Monday, May 23, 2022 7:06 AM
To: IACUC
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Compliance Report -- University of California Irvine D16-00259

Thank you for this report, (b) (6) We will send a response soon.

Axel Wolff, M.S., D.V.M.
Deputy Director, OLAW

From: IACUC <iacuc@uci.edu>
Sent: Friday, May 20, 2022 10:56 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Pramod Khargonekar <pramod.khargonekar@uci.edu>; Nancy Burley (UCI) <ntburley@uci.edu>; Claire Lindsell <claire.lindsell@uci.edu>; (b) (6)
Subject: [EXTERNAL] Compliance Report -- University of California Irvine D16-00259

Please see attached compliance self-report.

A preliminary report was not submitted to OLAW regarding this incident. All details, including correction plan, are included in the attached letter.

(b) (6)