



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

October 15, 2021

Re: Animal Welfare Assurance
A3431-01 [OLAW Case 9H]

Dr. Lisa Muto
Executive Dean for Administration
Harvard Medical School
25 Shattuck Street, Gordon Hall – (b) (4)
Boston, MA 02115

Dear Dr. Muto,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your September 29, 2021 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the Harvard Medical School following up on an initial February 3, 2021 notification by email.

According to the information provided, this Office understands that the Harvard Medical School Animal Care and Use Committee (ACUC) determined that instances of noncompliance occurred with respect to: failure to adhere to institutional policies and procedures, use of expired analgesics, failure to adhere to the IACUC-approved protocol and the conduct of animal-related activities without prior IACUC review and approval. The interim report dated August 12, 2021 stated that investigative results of the IACUC revealed the following findings:

- Mouse transport duration exceeded transportation guidelines.
- Mice were anesthetized with isoflurane when protocol states ketamine/xylazine will be used.
- Mice were anesthetized using open-drop method of isoflurane instead of a precision vaporizer for surgery.
- Mice did not receive multi-modal analgesia following surgery as required by the protocol.
- Lab members were not performing secondary methods of euthanasia as required.
- Off protocol procedures were being performed in the lab, including cardiac puncture, blood draws, and non-survival surgery.
- Expired buprenorphine was used on at least 3 different occasions following survival surgery.

These findings were discussed at the December 2020 IACUC meeting and updates were discussed at all subsequent monthly IACUC meetings. It is stated the IACUC sent the principal investigator (PI) a letter that included several requirements. Corrective actions included: assurance that animal users are familiar with all aspects of the approved IACUC protocol and understand that unapproved procedures or alternatives cannot be performed until reviewed and approved by the IACUC, installation of proper equipment and ensuring peri-operative components of surgery are performed appropriately with regards to animals' health and well-being and identifying a lab manager.

The final report states the PI responded to the IACUC letter and confirmed that no procedures other than breeding, genotyping and euthanasia will be conducted until the following actions occur:

- The lab will complete all required training for individuals working with animals.
- The lab will request specific hands-on training for any proposed procedure.
- The lab will arrange for direct veterinary supervision of the initial group of animals.

It is understood the IACUC is satisfied with the above corrective action plan and considers the matter resolved. It is also understood this research project is supported by PHS funding and the institution will ensure applicable costs paid from the NIH grant will be removed and the Institute/Center will be notified, as appropriate.

Based on its assessment of this explanation, OLAW understands that the Harvard Medical School has implemented appropriate measures to correct and prevent recurrences of these problems and is now compliant with provisions of the PHS Policy.

We appreciate being informed of these matters and find no cause for further action by this Office.

Sincerely,

**Jacquelyn
T. Tubbs -S**

Digitally signed by:
Jacquelyn T. Tubbs -S
Date: 2021.10.15
07:50:58 -04'00'

Jacquelyn Tubbs, DVM, DACLAM
Animal Welfare Program Specialist
Division of Compliance Oversight
Office of Laboratory Animal Welfare

cc: IACUC Contact



HARVARD MEDICAL SCHOOL

LISA M. MUTO, PH.D.
EXECUTIVE DEAN FOR ADMINISTRATION
HARVARD MEDICAL SCHOOL
25 SHATTUCK STREET, SUITE 408
BOSTON, MA 02115

September 29, 2021

Brent Morse, DVM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
Rockledge 1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982

FINAL REPORT

RE: Non-Compliance Report: Assurance: **A3431-01**
Harvard Medical Area Standing Committee on Animals (HMA IACUC)
Species: Mouse **Grant:** 5R01CA233558-02

Dear Dr. Morse,

This letter serves as a final report on a noncompliance that was preliminarily reported to OLAW on February 3, 2021 and updated August 12, 2021 by the Harvard Medical Area Standing Committee on Animals (HMA IACUC).

Since the update on August 12, 2021, the PI responded to an IACUC letter confirming that no procedures other than breeding, genotyping, and euthanasia will be performed until the following actions are taken:

1. The lab will complete all required training for individuals working with animals
2. The lab will request specific hands-on training for any proposed procedure
3. The lab will arrange for direct veterinary supervision of the initial group of animals

In addition, the institution will ensure that applicable costs paid from the NIH grant will be removed, and the Institute/Center (IC) supporting the award will be notified, as appropriate.

The Committee is satisfied with the corrective actions mentioned above and detailed in the update to the preliminary report letter dated August 12, 2021 and considers this incident to be resolved. Please let us know if any additional information is required at this time.

Sincerely,

(b) (6)

Lisa M. Muto, PhD
Executive Dean for Administration
HMA Institutional Animal Care & Use Committee: Institutional Official

CC: **Gerald B. Pier, PhD**
Chairman, Harvard Medical Area Standing Committee on Animals



(b) (6)

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Friday, October 1, 2021 7:25 AM
To: HMS-IACUC
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Final Report

Thank you for this report. We will send a response soon.

Axel Wolff, M.S., D.V.M.

Deputy Director, OLAW

From: HMS-IACUC <iacuc@hms.harvard.edu>
Sent: Wednesday, September 29, 2021 2:58 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: Final Report

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Friday, August 13, 2021 7:22 AM
To: HMS-IACUC
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Update on preliminary report

Thank you for this update. We will add it to the case file and look forward to receiving the final report from the IO after the IACUC has completed this investigation.

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

From: HMS-IACUC <iacuc@hms.harvard.edu>
Sent: Thursday, August 12, 2021 12:52 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: Update on preliminary report

Dear Dr. Morse,

The following is an update on the preliminary report we sent on February 3, 2021. On December 2, 2020, the Office of the IACUC received a whistleblower complaint about a lab's treatment of mice. The complaint was immediately investigated, with IACUC members and veterinary staff interviewing all lab members. The interviews and subsequent communication with the PI led to the discovery of a number of issues in the lab, including:

1. Mouse transport duration exceeding transportation guidelines
2. Mice anesthetized with isoflurane when protocol says ketamine/xylazine will be used
3. Mice anesthetized using open-drop method of isoflurane instead of a precision vaporizer for surgery
4. Mice not receiving multi-modal analgesia following surgery as required by the protocol
5. Lab members not performing secondary methods of euthanasia as required
6. Off protocol procedures being performed in the lab, including cardiac puncture, blood draws, and non-survival surgery
7. Expired buprenorphine was used on at least 3 different occasions following survival surgery

The PI voluntarily suspended all animal work except breeding, genotyping, and euthanasia following the investigation. The issues were first discussed at the December 2020 IACUC meeting and updates on the situation have been discussed at all subsequent monthly IACUC meetings. The outcomes following each meeting are detailed below.

Following the December IACUC meeting:

- The IACUC sent PI a letter that included a number of requirements, including assurance that animal users are familiar with all aspects of the approved IACUC protocol and understand that unapproved procedures or alternatives cannot be performed until reviewed and approved by the IACUC, installation of proper equipment and ensuring perioperative components of surgery are performed appropriately with regards to animals' health and wellbeing, and identifying a lab manager. The PI addressed these requirements in a letter to the IACUC.
- The PI and all lab members retook all required online IACUC and controlled substances training.
- The facility veterinarian met with lab members to review the noncompliance issues as well as related institutional animal care and use requirements.

- The Office of Regulatory Affairs and Research Compliance (ORARC) performed an audit of the lab.

Following the January 2021 IACUC meeting:

- The PI designated a lab manager
- A member of ORARC met with the PI and lab manager to discuss expectations for PI oversight and establishing a plan for onboarding new lab members.

Following the February 2021 IACUC meeting:

- The IACUC sent the PI a letter requesting an update on the outstanding issues, including how training would occur for lab-specific procedures, determining the new lab manager's confidence with the duties expected to be performed, and provide a status update on the hiring of new personnel

Following the March 2021 IACUC meeting:

- All lab members have left the lab except for the lab manager
- The PI plans to recruit new lab members later in the summer
- The IACUC asked the PI to remove any discontinued projects from the protocol

Following the April 2021 IACUC meeting:

- The lab manager received training from veterinary staff on how to use an isoflurane vaporizer, waste anesthetic gas control and scavenge, monitoring, assessing pain signs in mice, maintaining homeostasis, and analgesics
- The PI removed some procedures that are no longer being performed from the protocol
- The IACUC sent the PI a letter to determine which experiments the lab intended to carry out initially

Following the May 2021 IACUC meeting:

- IACUC members verified that the lab's CO2 euthanasia station was set up appropriately
- The PI described which experiments the lab would conduct initially
- The PI intended to serve as the back-up to the lab manager and would need to undergo in-person training with veterinary staff
- The PI was sent a letter by the IACUC to request approval for each experimental model individually, so that the IACUC may verify the following actions:
 1. Completion of all required online training for individuals working with animals
 2. Request of specific hands-on training for proposed procedures
 3. Arrangement of direct veterinary supervision for the initial group of animals

Following the June 2021 IACUC meeting:

- The PI received training from veterinary staff on handling, restraint, injections, blood collection, and euthanasia
- PI and lab manager were observed conducting CO2 euthanasia
- The PI said the lab is currently focusing on in-vitro studies

A final report will be sent following the IACUC's August 2021 meeting when all corrective actions have been taken and outstanding issues have been addressed.

Sincerely,

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(b) (6)

A3431-9H

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Wednesday, February 3, 2021 10:04 AM
To: HMS-IACUC
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Preliminary Report

Thank you for this preliminary report, (b) (6) We will start a new case file and look forward to receiving the final report from the IO after the IACUC has completed its investigation.

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

From: HMS-IACUC <iacuc@hms.harvard.edu>
Sent: Wednesday, February 3, 2021 9:21 AM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: Preliminary Report

Dear Dr. Morse,

We would like to preliminarily report an issue that was first conveyed to the Office of the IACUC in December 2020. The complaint the Office received led to a comprehensive and ongoing investigation, including interviews with all lab members. Several findings have been uncovered including off-protocol procedures, inappropriate/inadequate anesthesia and analgesia, non-compliance with euthanasia and animal transportation requirements, and use of expired buprenorphine. The PI has voluntarily stopped all procedures except breeding, genotyping, and euthanasia while the investigation is ongoing. We will send a final report providing further details once all the corrective actions have been implemented.

Sincerely,

(b) (6)

