



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

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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

March 9, 2022

Re: Animal Welfare Assurance
#A3284-01 (OLAW Case 2V)

Dr. Jill C. Pipher
Vice President for Research
Brown University
47 George St. - Box 1937
Providence, Rhode Island 02912

Dear Dr. Pipher,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your February 23, 2022 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the Brown University. This letter had not been preceded by a preliminary report to OLAW.

According to the information provided, this Office understands that the Brown University Animal Care and Use Committee (ACUC) determined that instances of noncompliance occurred with respect to: failure to adhere to the IACUC-approved protocol. The final report states on January 26, 2022, six mice developed signs of morbidity following intrathecal administration of hydrochloric acid (HCl). The animals were identified by husbandry staff and were euthanized by a Center for Animal Resources and Education (CARE) veterinarian. It is stated another animal was found dead the following day. It was determined a student had administered 50uL of 0.7M HCl, but the protocol is approved for only 40uL. It is also stated the student did not recognize the humane endpoints described in the protocol during monitoring and did not notify the veterinary staff or other lab members of the adverse experimental outcome.

Per the report, the IACUC discovered that the student observed a similar unanticipated experimental outcome at least one time prior to this incident. According to the lab, all animals recovered during the first incident. Ultimately, it was determined the lab members administered the incorrect dose of HCl for the past several months.

The matter was reviewed by the IACUC on February 4, 2022, and the committee required the following corrective actions:

- The laboratory must amend the protocol as follows:
 - Perform a pilot study to determine the lowest effective concentration of HCl and reduce the concentration in the protocol accordingly.
 - Include a description of possible morbidity and the respiratory monitoring parameters from the HCl intratracheal procedure as humane endpoints.
 - Perform a pH check of the solution prior to performing the experiment each time.
 - Increase the frequency of post-procedural monitoring.
- The laboratory was reminded to refer to the approved protocol during procedures and to always keep an updated copy of the protocol in the laboratory. The laboratory may institute a standard protocol review meeting with lab members.

- All laboratory members must undergo retraining on appropriate humane endpoints, veterinary care and animal use, and prompt reporting of unanticipated events.
- The laboratory must work with CARE to develop a numerical or other objective scoring sheet to be used during post-procedural monitoring.
- A CARE veterinarian will oversee all intratracheal procedures until consistent and satisfactory technique and post-procedure monitoring are achieved.
- The laboratory must utilize older mice in future experiments.

It is noted that this research is supported by PHS funding. Based on its assessment of this explanation, OLAW understands that the Brown University 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: 2022.03.09 09:13:34
-05'00'

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

cc: IACUC Contact

**BROWN**

February 23, 2022

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

RE: Report of noncompliance, Assurance #A3284-01
Grant: 5R01HL126887-04-Noa

Dear Dr. Morse:

The Brown University Institutional Animal Care and Use Committee (IACUC), through the Institutional Official (Jill C. Pipher, Ph.D.), is writing to provide OLAW with a final report of the following noncompliance with the *PHS Policy on Humane Care and Use of Laboratory Animals* ("PHS Policy"):

On January 26, 2022, 6 mice became moribund following intratracheal administration of hydrochloric acid (HCl). The mice were discovered by husbandry staff and were euthanized by a Center for Animal Resources and Education (CARE) veterinarian. Another mouse was found deceased the following day. The student performing the experiment had administered 50uL of 0.7M HCl, though the protocol is approved for only 40uL. Further, the student failed to recognize the humane endpoints listed in the protocol during monitoring and did not alert the veterinary staff or other lab members of the adverse experimental outcome

During the meeting, the IACUC learned that the student observed a similar unanticipated experimental outcome at least one time prior to this event. It was stated by the lab that all animals did recover during the first incident. Further, it was determined that members of the lab have been administering the incorrect dose of HCl for the past several months.

The IACUC discussed the incident of animal welfare concern at its February 4, 2022 convened meeting, and determined that the incident meets the criteria for reporting per the NIH NOT-OD-05-034, "Guidance on Prompt Reporting to OLAW under the PHS Policy on Humane Care and Use of Laboratory Animals."

The following corrective actions have taken, or will take, place:

- The laboratory must amend the protocol as follows:
 - Perform a pilot study to determine the lowest effective concentration of HCL and reduce the concentration in the protocol accordingly.
 - Include a description of possible morbidity and the respiratory monitoring parameters from the HCL Intratracheal procedure as humane endpoints.
 - Perform a pH check of the solution prior to performing the experiment each time.

- Increase the frequency of post-procedural monitoring.
- The laboratory was reminded to refer to the approved protocol during procedures and to keep an updated copy of the protocol in the laboratory at all times. The laboratory may institute a standard protocol review meeting with lab members.
- All laboratory members must undergo retraining on appropriate humane endpoints, veterinary care and animal use, and prompt reporting of unanticipated events.
- The laboratory must work with CARE to develop a numerical or other objective scoring sheet to be used during post-procedural monitoring.
- A CARE veterinarian will oversee all intratracheal procedures until consistent and satisfactory technique and post-procedure monitoring is achieved.
- The laboratory must utilize older mice in future experiments

Brown University is committed to protecting the welfare of animals used in research and appreciates the guidance and assistance provided by OLAW in this regard. If you have any questions or concerns regarding this report, please contact (b) (6)

Thank you for your consideration of this matter.

Sincerely,

(b) (6)

Jill C. Pipher, Ph.D.
Vice President for Research, Institutional Official Brown
University

cc: Diane Hoffman-Kim, PhD, IACUC Chair

(b) (6)

Lara Helwig, DVM, Director of CARE, Attending Veterinarian
AAALACi

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Wednesday, February 23, 2022 11:08 AM
To: IACUC
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: [EXTERNAL] Report of noncompliance, Assurance #A3284-01

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

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

From: (b) (6) On Behalf Of IACUC
Sent: Wednesday, February 23, 2022 10:58 AM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: [EXTERNAL] Report of noncompliance, Assurance #A3284-01

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and are confident the content is safe.

Good afternoon,

Please find attached a report regarding an incident of noncompliance discussed by the Brown University IACUC during its February 4, 2022 convened meeting.

Please let us know if you have any questions.

Thanks,

(b) (6)