



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

February 7, 2022

Re: Animal Welfare Assurance
A3646-01 [OLAW Case 1W]

Dr. Jon Reuter
Assistant Vice Chancellor for Research Integrity and Compliance
University of Colorado – Boulder
3100 Marine Street, UCB 563 (b) (4)
Boulder, CO 80309

Dear Dr. Reuter,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your March 10, 2022 response to my February 7, 2022 request for additional information regarding an unapproved action taken by the Institutional Animal Care and Use Committee (IACUC) at the University of Colorado- Boulder. According to the information provided, OLAW understands the following:

- 1) The laboratory involved was counseled to euthanize the rats involved.
- 2) The Principal Investigator (PI) was counseled on not using data, collected under unapproved conditions, for submission to a journal.
- 3) The PI was notified not to charge the grant for any unauthorized animal activities and the Grants office was also notified. (OLAW note: see also NIH Guidance
<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-081.html>
<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-044.html>)
- 4) The PI was notified that the pilot study that had been incorrectly approved by the IACUC was not valid.
- 5) The PI added contingency plans to the study, including administration of fluids during surgery, to avoid future adverse events. Animal procedures were modified and only fresh experimental agents will be used. The PI assured the IACUC that such an incident would not recur and that laboratory staff is aware that only approved procedures may be conducted, as described in the protocol.
- 6) The PI and laboratory staff were counseled on the requirement to only perform IACUC approved animal activities. The laboratory was placed under enhanced post-approval monitoring.
- 7) The IACUC was apprised on the consequences of allowing the conduct of unapproved animal activities.

Based on its assessment of these explanations, OLAW understands that appropriate corrective actions have been taken to address all concerns and that measures have been implemented to prevent recurrence. Note that although euthanasia is usually warranted when animals cannot be appropriately used, it is possible to reassign them to an approved activity such as for training. We note this so that a future mistake does not lead to immediate euthanasia if an acceptable alternative is available. The IACUC is always welcome to contact this Office with any questions on the application of the PHS Policy on Humane Care and Use of Laboratory Animals. Thank you for keeping OLAW apprised on this matter.

Sincerely,

(b) (6)

Axel Wolff, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare

cc: IACUC Chair



University of Colorado
Boulder

Jon Reuter, Assistant Vice Chancellor for
Research Integrity and Compliance
4845 Pearl East Circle, room 206 (UCB 563)
Boulder, CO 80309

jon.reuter@colorado.edu

t 303 735-5809

March 10, 2022

Axel Wolff, DVM
Deputy Director, Division of Compliance
Oversight Office of Laboratory Animal
Welfare National Institutes of Health
6700B Rockledge Drive, Suite 2500 MSC 6910
Bethesda, MD 20892

Dr. Wolff,

The University of Colorado Boulder, Assurance No. D16-00388, provides the following response to your letter of February 7, 2022 regarding Animal Welfare Assurance A3646-01 [OLAW Case 1W].

Protocol: 2611
Funds: NIH RMH050479G & NIH RMH116353A

Species: Rats

Responses to the seven prohibitions and questions outlined in your letter are as follows:

1. The IACUC recognizes it does not have the authority to retroactively approve an animal activity. We apologize for any confusion regarding this and have notified the lab that the animals are to be euthanized.
2. The IACUC recognizes that use of data collected from a study that did not have initial IACUC approval is not accepted by most journals and the Principal Investigator was notified immediately at the time of occurrence.
3. Charges to the grant were not associated with this incident. The PI was immediately notified that any costs associated with this experiment were not to be charged back to the grant. The Grants office was notified.
4. The PI was notified that the pilot study was not approved, and the animals would need to be euthanized.
5. The IACUC Director met with the PI and worked with contingency plans that will be put into place in the event potential adverse consequences were to occur in the future as well as added steps for provision of fluids during and after surgery to mitigate risks. To address the situation, corrective actions were taken including the submission of an *Animal Study Protocol Amendment*. The PI expressed in a letter to the IACUC that this was an unfortunate incident and took responsibility for the noncompliance. The PI assured the IACUC that an incident of such nature would not occur again. The PI has also assured the IACUC that all research staff will from now on carefully review and adhere to approved study protocols.
6. The IACUC Director met with the PI and his lab members providing training of what is approved in the protocol, the seriousness of conducting unapproved experiments and consequences of conducting unapproved experiments. The surviving animals involved were euthanized. In addition, a post-approval monitoring (PAM) of the protocol was put into place where surgical procedures were reviewed.

7. A meeting was held with IACUC Committee Members. Topics of material distributed to the IACUC Committee Members included information provided from OLAW regarding the fact that unapproved procedures cannot be approved retroactively. Members were apprised that animals undergoing an unapproved procedure must be euthanized. Although it was the committee's intent to save the remaining animals it was conveyed to them that this is not an acceptable solution, and that data received from the animals is not publishable.

CU Boulder maintains its commitment to the health and welfare of animals used in research. Should you have any questions regarding this report, please contact Christopher A. Lowry, PhD, IACUC Chair at christopher.lowry@colorado.edu or (b) (6)

Sincerely,

(b) (6)

Jon Reuter, Assistant Vice Chancellor of Research Integrity and Compliance

Cc:

Christopher A. Lowry, IACUC Chair

(b) (6)

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Wednesday, March 16, 2022 7:28 AM
To: (b) (6)
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: OLAW Case 1W - CU Boulder

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

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

From: (b) (6)
Sent: Tuesday, March 15, 2022 10:44 AM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: [EXTERNAL] FW: OLAW Case 1W - CU Boulder

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.

From: (b) (6)
Sent: Tuesday, March 15, 2022 8:43 AM
To: OLAW-DOA Annual Reports (NIH/OD) <olawarp@od.nih.gov>
Subject: OLAW Case 1W - CU Boulder

Dear OLAW,

Please see the attached letter in response to your letter dated February 7, 2022 (OLAW Case 1W). We also wish to convey that veterinary oversight was involved. As an addition to number 5, the lab plans to use fluid and fresh ibotenate for future injections rather than frozen stocks, and they will inject across two areas of the brain rather than one, in order to minimize possible toxicity in a larger brain region.

Please advise if you have further questions,

(b) (6)

Ward, Joan (NIH/OD) [E]

From: Christopher Lowry <christopher.lowry@colorado.edu>
Sent: Wednesday, February 9, 2022 8:47 AM
To: Ward, Joan (NIH/OD) [E]; Jon D Reuter
Cc: [REDACTED] (b) (6)
Subject: [EXTERNAL] RE: OLAW Case A3646-1W
Attachments: 0344_001.pdf

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.

Bringing in [REDACTED] (b) (6) as this may require a rapid response, particularly this part (there is more, see letter attached).

- 1) The IACUC does not have the authority to retroactively approve an animal activity. As such, the use of the rats following the unauthorized application of an unapproved agent is not permissible.

Best wishes,
Chris

From: Ward, Joan (NIH/OD) [E] <wardjoa@od.nih.gov>
Sent: Wednesday, February 9, 2022 6:30 AM
To: Jon D Reuter <Jon.Reuter@Colorado.EDU>
Cc: Christopher Lowry <christopher.lowry@colorado.edu>
Subject: FW: OLAW Case A3646-1W

Dear Dr. Reuter,

Attached please find Dr. Wolff's initial response to OLAW Case A3646-1W.

If you have any questions, feel free to contact us by phone or by e-mail.

Best Regards,
Joan

Joan Ward
Program Specialist
Office of Laboratory Animal Welfare
National Institutes of Health
6700B Rockledge Dr., Suite 2500
Bethesda, MD 20892
301-496-7163
wardjoa@od.nih.gov

Note: To protect against computer viruses, e-mail programs may prevent sending or receiving certain types of file attachments. Check your e-mail security settings to determine how attachments are handled.



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

February 7, 2022

Re: Animal Welfare Assurance
A3646-01 [OLAW Case 1W]

Dr. Jon Reuter
Assistant Vice Chancellor for Research Integrity and Compliance
University of Colorado – Boulder
3100 Marine Street, UCB 563 (b) (4)
Boulder, CO 80309

Dear Dr. Reuter,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your February 4, 2022 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the University of Colorado- Boulder, following up on an initial report on January 26, 2022. According to the information provided, OLAW understands that six rats were given an agent not approved on the protocol and three animals experienced adverse reactions which necessitated euthanasia. The three remaining rats returned to health and the Principal Investigator requested continued use of the animals for the study.

The corrective actions consisted of counseling the PI to ensure that all animal activities have received prior Institutional Animal Care and Use Committee (IACUC) approval. The IACUC approved a behavioral pilot study with the same rats which had received the unapproved agent.

Please note the following prohibitions and questions:

- 1) The IACUC does not have the authority to retroactively approve an animal activity. As such, the use of the rats following the unauthorized application of an unapproved agent is not permissible.
- 2) The use of data collected from a study that did not have initial IACUC approval is not accepted by most journals and the lack of IACUC approval needs to be disclosed.
- 3) The procedures using the unauthorized agent are not to be charged to the grant.
- 4) Approval of a pilot study prior to initiation is allowed, however, in this case the animals were already “wasted” in that an unapproved activity had been conducted. Allowing the unapproved study to proceed by approving a pilot study after the fact, is not permissible.
- 5) What actions were taken to prevent or reduce the likelihood of adverse events caused by the unapproved agent?
- 6) Indicate how the IACUC has resolved this entire situation regarding the unapproved agent, the actions taken with the surviving rats, and measures taken to prevent a recurrence.

Page 2 – Dr. Rueter
February 7, 2022
OLAW Case A3646-1W

- 7) Indicate how the IACUC will ensure that unapproved procedures are not approved retroactively and how this information has been disseminated to the investigators.

Please provide the requested information by **March 15, 2022**. Feel free to contact me should you have any questions.

Sincerely,

 (b) (6)

Axel Wolff, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare

cc: IACUC Chair

Jon Reuter, Assistant Vice Chancellor for
Research Integrity and Compliance
4845 Pearl East Circle, room 206 (UCB 563)
Boulder, CO 80309

jon.reuter@colorado.edu

t 303 735-5809



University of Colorado
Boulder

February 4, 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 20892

Dr. Morse,
The University of Colorado Boulder, Assurance No. D16-00388, provides the following non-compliance report outlined below. Please note a preliminary report was provided on 1/26/2022 by

(b) (6)

Protocol: 2611
Funds: NIH RMH050479G & NIH RMH116353A

Species: Rats

On 1/26/22 an unapproved agent was given during an approved surgery. After the surgery the animals experienced unanticipated adverse effects that resulted in three of the six animals being euthanized. The three remaining animals were closely monitored and returned to normal health. The lab was repeating an experiment done in years prior in order to collect additional data, and the PI did not realize the agent had been removed from the protocol.

The IACUC office discussed with the principal investigator the importance of reviewing the protocol to be sure all procedures and agents are approved. The PI requested to continue to use the three remaining animals for planned non-invasive behavioral testing following the surgery. The behavioral testing is an approved procedure on the protocol. The IACUC met in a special meeting to discuss the PI's request. After discussion, the committee determined that letting the PI continue to use these animals as a pilot study and subsequently utilize the histology to determine what occurred in this cohort would be useful to the lab. The PI has submitted an amendment for a pilot study of the behavioral testing portion of the experiment. Pending the results of the pilot, the PI can submit an amendment to add the study with the agent to the protocol to be performed to supplement historical data.

CU Boulder maintains its commitment to the health and welfare of animals used in research. Should you have any questions regarding this report, please contact Christopher A. Lowry, PhD, IACUC Chair at christopher.lowry@colorado.edu or

(b) (6)

(b) (6)

Sincerely,

(b) (6)

Jon Reuter, Assistant Vice Chancellor of Research Integrity and Compliance

Cc:
Christopher A. Lowry, IACUC Chair

(b) (6)

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Monday, February 7, 2022 7:15 AM
To: IACUC Office
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Reportable Incident

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

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

From: IACUC Office <iacucoffice@colorado.edu>
Sent: Friday, February 4, 2022 12:08 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Jon D Reuter <Jon.Reuter@Colorado.EDU>; (b) (6) Christopher Lowry
<christopher.lowry@colorado.edu>; (b) (6)
Subject: [EXTERNAL] Reportable Incident

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.

Dear OLAW,

Please find attached the final report for an incident that we have found reportable. A preliminary report was sent on 1/26/2022.

Thank you,

(b) (6)

A3646-1W

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Friday, January 28, 2022 7:19 AM
To: IACUC Office
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Preliminary Report on a Non-Compliance

Thank you for this preliminary report. We will open a new case file and look forward to receiving the final report from the IO after the IACUC has completed its investigation. Please remember to indicate the species involved and the funding source.

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

From: IACUC Office <iacucoffice@colorado.edu>
Sent: Wednesday, January 26, 2022 5:20 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: (b) (6)
Subject: [EXTERNAL] Preliminary Report on a Non-Compliance

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,

I am (b) (6) I am emailing to provide preliminary information on a non-compliance. The non-compliance involved the use of an experimental agent that was not approved in the current protocol during an approved procedure. Due to the condition of the animals following the procedure the Attending Veterinarian required euthanasia of the animals involved. We are currently still investigating this non-compliance and gathering information. Our IACUC committee will convene in February to review the findings from the investigation. After the committee convenes a letter will be sent to OLAW with further information and the resolution.

CU Boulder's Assurance number is D16-00388 (A3646-01)

Thank you,

(b) (6)