



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) 402-7065

February 28, 2019

Re: Animal Welfare Assurance
A3448-01 [OLAW Case Z]

Dr. Yvonne T. Maddox
Vice President for Research and
Institutional Official
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814

Dear Dr. Maddox,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your February 7, 2019 letter regarding noncompliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals. The preliminary report of this incident was made by email to OLAW on July 19, 2018. According to the information supplied, OLAW understands that on July 12, 2018 the IACUC received information regarding procedures that were not completed in accordance with the IACUC-approved protocol. These allegations were later confirmed by the principal investigator (PI) and research staff. Laboratory members had engaged in unapproved handling and unapproved conduct of treadmill testing with rats that resulted in an increased level of stress or distress experienced by the animals when compared to the approved procedures. It was also noted that an unapproved method of toe clipping for identification was used. The funding agency, Uniformed Services University in the Department of Defense, and the Animal Care and Use Research Office were informed.

Corrective actions included immediately halting all work on the protocol while an investigation was undertaken by an IACUC subcommittee. After discussion of the IACUC subcommittee's findings, the IACUC voted to suspend the protocol on July 18, 2018 and decided that if the PI wished to conduct any work on the protocol, new investigator training must be completed by the PI and a new protocol must be reviewed and approved by the IACUC.

Please note that OLAW requests submission of the final report once action has been taken. For all future reporting, please ensure submission of the preliminary report followed by timely submission of the final report after the IACUC has determined how the incident will be addressed. OLAW concurs with the IACUC action to prevent recurrence of this incident. Additional actions to address similar incidents on a programmatic level should be undertaken to enhance or verify PI and researcher understanding of the roles and responsibilities of animal care and use and of the requirement for adherence to the IACUC-approved protocol prior to protocol approval. The research team should have the necessary knowledge prior to being permitted to proceed with animal use. We appreciate being informed of these matters and find no cause for further action by this Office at this time.

Page 2 – Dr. Maddox
February 28, 2019
OLAW Case A3448-Z

Sincerely,

(b) (6)

Jane Na, DVM
Veterinary Medical Officer
Office of Laboratory Animal Welfare

cc: IACUC Contact



UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4712



February 7, 2019

Axel Wolff M.S., D.V.M.
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
RKL1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda MD 20892-7982

Dear Dr. Wolff,

Final Incident Report - (OLAW Assured Facility Number A3448-01)

This is a final report on an incident at Uniformed Services University of the Health Sciences (USU) (OLAW Assured Facility Number A3448-01) that was initially reported to the Office of Laboratory Animal Welfare (OLAW) on 18 July 2018.

The USU IACUC received information on Thursday 12 July from a staff member concerning a possible deviation from an approved protocol. It was suggested that procedures not described in the approved protocol were being conducted in an ongoing study. This protocol involved stressing rats by running them on a treadmill and examining treatments that might improve exercise capacity. In order to encourage the rats to perform on the treadmill, the approved protocol permitted the delivery of a mild shock (0.5 mA, 1 Hz, for no more than 5 sec) if they left or fell off the treadmill, encouraging them to move back onto the treadmill. Concerns were raised with respect to how the treadmill study was being conducted.

In view of the potential seriousness of the allegations, the IACUC Chair spoke briefly with the initial reporting staff member and two other persons who had also raised concerns independently of the initial report. The Chair then informed the PI and the Attending Veterinarian and his deputy that no further procedures could be conducted under this protocol while the allegations were investigated. No additional procedures were conducted under this protocol after 12 July 2018.

An IACUC subcommittee was appointed to review the incident. Subcommittee members reviewed the approved animal research protocol and discussed what was observed with the three persons who had raised concerns. One person reported noticing frequent and lengthy animal distress noises in a central procedure room on multiple occasions over several months. These noises were audible from the hallway even with the door of room closed. He reported on one occasion doing a slow count to 30 seconds while hearing the noises continuously, leading him to believe that animals were being shocked for periods in excess of 5 seconds. He also reported regular, loud banging during testing. He also reported observing tests through the hallway peephole, noticing that the technician administering the test was lifting the treadmill used in the protocol to cause animals to fall back onto the treadmill. The observer then entered the room and questioned the technician, suggesting that the procedures

being performed were inappropriate. He contacted the PI and suggested that the methods being used were inconsistent with good practice. The observer reported that he felt the PI was not appropriately responsive to his concerns.

The subcommittee also interviewed two other concerned researchers working in adjacent rooms who supported the report of frequent and lengthy vocalizations from the procedure room that were audible from the hallway. Subcommittee members then met with the PI and two of his animal handlers (Research Associates) to discuss these issues. During this discussion the PI freely admitted to several aspects of routine animal handling procedures that were either not discussed in the approved protocol or were direct deviations from the approved procedures. The subcommittee also found evidence of deviations from the approved mild shock protocol, the use of non-approved methods including mechanical prodding and banging on the apparatus to keep rats running on the treadmill, and unapproved toe nail clipping for animal identification.

The subcommittee reported to the IACUC that there was clearly sufficient evidence, much of it self-reported by the PI, to demonstrate multiple violations of IACUC protocol and policies. The violations did not appear to be malicious in nature or to reflect a knowing disregard for the rules but seemed to occur due to either a profoundly inadequate understanding of what needed to be covered by an IACUC protocol and/or a misunderstanding of what was approved under the protocol. There was insufficient evidence to conclusively support the most serious allegation, namely the shocking of animals over long periods of time (in excess of 5 sec). However, the deviations in shock intensity and unapproved encouragement methods represent a clear increase in the level of stress/distress to which the animals were exposed relative to procedures approved in the protocol.

The report of the subcommittee was discussed by the full IACUC at its scheduled meeting on 18 July 2018. The PI was invited to attend the meeting, where he presented a defense of his actions under the protocol, and then left the room. After consideration of the results of the subcommittee investigation, review of the approved protocol, and the presentation by the PI, the IACUC voted unanimously to suspend the protocol effective immediately.

The following protocol deviations and animal welfare concerns were noted:

- The PI reported that they were using 1.5 mA shocks at 2 Hz to encourage running; however, the approved protocol allowed a maximum of 0.5 mA at 1 Hz. Subsequent examination by the subcommittee and re-calibration of the equipment by the PI suggested that the amperage used was actually slightly below 0.5 mA (although the PI had intended to set the current to 1.5 mA). The PI did not dispute that the frequency was set at 2 Hz.
- The Committee was made aware of concerns from bystanders regarding excessive and prolonged vocalization from animals in the PI's laboratory. This suggested to the bystanders and the subcommittee that the rats were possibly being subjected to undue stressors or to shock for periods in excess of the 5 second exposure to 0.5 mA, 1 Hz mild electric shock described in the approved protocol. The PI rejected contentions by bystanders outside the room that he had permitted rats to receive electrical shocks for periods as long as 30 sec. claiming that since more than one treadmill was in use simultaneously, the vocalizations over periods exceeding 5 secs that were reported to the subcommittee in fact originated from different rats. The subcommittee was unable to determine whether prolonged shock duration was used on some occasions.

- One of the study team members admitted to unapproved tilting and jostling of the entire treadmill apparatus on multiple occasions in order to eject rats onto the already running treadmill. This was reportedly done to compensate for a known equipment failure of the shock apparatus.
- Study team members reported regular unapproved touching of animals and prodding with a stick from below the cage to encourage rats to move back onto the treadmill.
- The PI and study team members reported frequent unapproved banging on the apparatus walls to startle animals into returning to the treadmill.
- The PI reported unapproved handling of rats for the purpose of clipping toe nails for animal identification.
- Committee members noted that completion of study procedures on the remaining set of rats in full accordance with the approved protocol would require the use of procedures that differed significantly from those actually applied in the initial round of experiments. Concerns were expressed that data obtained from completing these studies would therefore not be usable or have statistical significance and validity. This also cast doubt on the PI's ability to publish the results of this study.
- Committee members were also concerned that the PI did not appear to understand his responsibilities to adhere to the detailed methods described in the approved protocol. Nor did he appear to understand the ethical implications of exposing animals to inescapable pain and distress, and the differences between subjecting animals to excessive inescapable stress and the stress experienced voluntarily by exercising humans.

The IACUC voted to suspend authorization to conduct any work under this protocol from the date of the IACUC meeting; no additional work can be conducted under this protocol.

Remaining rats held under the protocol were transferred to another protocol. The PI was informed that if he wishes to initiate animal work in the future he must again complete all training requirements for a new investigator and must submit a new animal research protocol for review and approval by the IACUC.

The funding source for the suspended project is an intramural research program at Uniformed Services University in the Department of Defense. The funding agency (USU), and the US Army Animal Care and Use Research Office (ACURO) has been informed of this decision. With these actions, we now consider this incident closed.

Sincerely,

(b) (6)

Yvonne T. Maddox, Ph.D.
Vice-President for Research, and
Institutional Official
Uniformed Services University

Morse, Brent (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Thursday, February 07, 2019 2:29 PM
To: (b) (6) OLAW Division of Compliance Oversight (NIH/OD)
Cc: Brian Cox; Yvonne Maddox; (b) (6)
Subject: RE: Reportable Event - Final Report - USUHS

Thank you for providing this report (b) (6) We will send an official response soon.

Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

Please note that this message and any of its attachments are intended for the named recipient(s) only and may contain confidential, protected or privileged information that should not be distributed to unauthorized individuals. If you have received this message in error, please contact the sender.

From: (b) (6)
Sent: Thursday, February 07, 2019 2:24 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Brian Cox <brian.cox@usuhs.edu>; Yvonne Maddox <yvonne.maddox@usuhs.edu>; (b) (6)
(b) (6)
Subject: Reportable Event - Final Report - USUHS

Good afternoon Dr. Morse,

Please see the attached final report regarding a deviation in July 2018.

Let me know if there are any questions.

Thank you,

(b) (6)

From: OLAW Division of Compliance Oversight (NIH/OD) [mailto:olawdco@od.nih.gov]
Sent: Wednesday, February 6, 2019 8:58 AM
To: OLAW Division of Compliance Oversight (NIH/OD); Megan Ralls
Cc: Brian Cox; (b) (6) Yvonne Maddox; (b) (6)
Subject: RE: Reportable Event - Preliminary Report - USUHS
Importance: High

Good morning,

OLAW has not received a response to the message below. Please confirm that you will be filing a final or interim report regarding this issue. Thank you.

Sincerely, Brent Morse

Good afternoon,

OLAW doesn't have a record of receiving a final report for this incident. If one is available, please provide it in an email response to this message. If not, please provide an interim report ASAP. Thank you.

Sincerely, Brent Morse

Brent C. Morse, DVM, DACLAM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

Please note that this message and any of its attachments are intended for the named recipient(s) only and may contain confidential, protected or privileged information that should not be distributed to unauthorized individuals. If you have received this message in error, please contact the sender.

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Thursday, July 19, 2018 1:44 PM
To: (b) (6) OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: USARMY Ft Detrick MEDCOM USAMRMC Other ACURO <usarmy.detrick.medcom-usamrmc.other.acuro@mail.mil>; Brian Cox <brian.cox@usuhs.edu>; (b) (6) Yvonne Maddox <yvonne.maddox@usuhs.edu>; (b) (6)
Subject: RE: Reportable Event - Preliminary Report - USUHS

Thank you for submitting this prompt preliminary report. We will open a case file and await further information.

Sincerely, Brent Morse

Brent C. Morse, DVM, DACLAM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

Please note that this message and any of its attachments are intended for the named recipient(s) only and may contain confidential, protected or privileged information that should not be distributed to unauthorized individuals. If you have received this message in error, please contact the sender.

From: (b) (6)
Sent: Thursday, July 19, 2018 1:38 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: USARMY Ft Detrick MEDCOM USAMRMC Other ACURO <usarmy.detrick.medcom-usamrmc.other.acuro@mail.mil>;
Brian Cox <brian.cox@usuhs.edu>; (b) (6)
(b) (6) Yvonne Maddox <yvonne.maddox@usuhs.edu>; (b) (6)
Subject: Reportable Event - Preliminary Report - USUHS

Dear Dr. Morse,
Attached is an initial incident report regarding a deviation from a protocol that occurred at Uniformed Services University. A final report will be submitted once the investigation has concluded.

Please let me know if you have any questions or concerns.
Thank you,

(b) (6)

Morse, Brent (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Wednesday, February 06, 2019 1:06 PM
To: Brian Cox; OLAW Division of Compliance Oversight (NIH/OD)
Cc: (b) (6)
Subject: RE: Reportable Event - Preliminary Report - USUHS

Thank you very much for this reply Dr. Cox. We look forward to receiving the final report.

Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

Please note that this message and any of its attachments are intended for the named recipient(s) only and may contain confidential, protected or privileged information that should not be distributed to unauthorized individuals. If you have received this message in error, please contact the sender.

From: Brian Cox [mailto:brian.cox@usuhs.edu]
Sent: Wednesday, February 06, 2019 9:55 AM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: (b) (6)
Subject: Re: Reportable Event - Preliminary Report - USUHS
Importance: High

Dr. Morse,

I apologize for the delay in getting the Final Report on this incident to you. I assure you that actions to prevent similar incidents were taken soon after the initial event, and the IACUC completed actions addressing the incident promptly. I will try to get the final report signed and submitted as soon as possible.

Sincerely,

Brian Cox Ph.D.
Chair, IACUC
Uniformed Services University
(b) (6)

On Feb 6, 2019, at 8:57 AM, OLAW Division of Compliance Oversight (NIH/OD)
<olawdco@od.nih.gov> wrote:

Good morning,

Morse, Brent (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Wednesday, February 06, 2019 8:58 AM
To: OLAW Division of Compliance Oversight (NIH/OD); Megan Ralls
Cc: Brian Cox; (b) (6) Yvonne Maddox; (b) (6)
Subject: RE: Reportable Event - Preliminary Report - USUHS

Importance: High

Good morning,

OLAW has not received a response to the message below. Please confirm that you will be filing a final or interim report regarding this issue. Thank you.

Sincerely, Brent Morse

Good afternoon,

OLAW doesn't have a record of receiving a final report for this incident. If one is available, please provide it in an email response to this message. If not, please provide an interim report ASAP. Thank you.

Sincerely, Brent Morse

Brent C. Morse, DVM, DACLAM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

Please note that this message and any of its attachments are intended for the named recipient(s) only and may contain confidential, protected or privileged information that should not be distributed to unauthorized individuals. If you have received this message in error, please contact the sender.

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Thursday, July 19, 2018 1:44 PM
To: (b) (6) OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: USARMY Ft Detrick MEDCOM USAMRMC Other ACURO <usarmy.detrack.medcom-usamrmc.other.acuro@mail.mil>; Brian Cox <brian.cox@usuhs.edu>; (b) (6) Yvonne Maddox <yvonne.maddox@usuhs.edu>; (b) (6)
Subject: RE: Reportable Event - Preliminary Report - USUHS

Thank you for submitting this prompt preliminary report. We will open a case file and await further information.

Sincerely, Brent Morse

Brent C. Morse, DVM, DACLAM
Director
Division of Compliance Oversight

A3448-2
Preliminary

18 Jul 2018

To Brent Morse, DVM, DACLAM, OLAW

Dr. Morse,

This is an initial report of an incident relating to the research animal care and use program at Uniformed Services University, Bethesda MD.

The USU IACUC received information on Thursday 12 July from a staff member concerning a possible deviation from an approved protocol. It was suggested that procedures not described in the approved protocol were being conducted in an ongoing study. The IACUC has appointed a subcommittee of the IACUC to investigate these allegations, and the investigation is now in progress.

A final report on the incident will be sent to OLAW when the incident has been resolved. Please contact us if you have any questions or concerns.

Contact person making report:



(b) (6)

Morse, Brent (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Thursday, July 19, 2018 1:44 PM
To: (b) (6) OLAW Division of Compliance Oversight (NIH/OD)
Cc: USARMY Ft Detrick MEDCOM USAMRMC Other ACURO; Brian Cox; (b) (6)
(b) (6) Yvonne Maddox; (b) (6)
Subject: RE: Reportable Event - Preliminary Report - USUHS

Thank you for submitting this prompt preliminary report. We will open a case file and await further information.

Sincerely, Brent Morse

Brent C. Morse, DVM, DACLAM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

Please note that this message and any of its attachments are intended for the named recipient(s) only and may contain confidential, protected or privileged information that should not be distributed to unauthorized individuals. If you have received this message in error, please contact the sender.

From: (b) (6)
Sent: Thursday, July 19, 2018 1:38 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: USARMY Ft Detrick MEDCOM USAMRMC Other ACURO <usarmy.detrick.medcom-usamrmc.other.acuro@mail.mil>; Brian Cox <brian.cox@usuhs.edu>; (b) (6)
(b) (6) Yvonne Maddox <yvonne.maddox@usuhs.edu>; (b) (6)
Subject: Reportable Event - Preliminary Report - USUHS

Dear Dr. Morse,
Attached is an initial incident report regarding a deviation from a protocol that occurred at Uniformed Services University. A final report will be submitted once the investigation has concluded.

Please let me know if you have any questions or concerns.
Thank you,

(b) (6)