



DEPARTMENT OF HEALTH & HUMAN SERVICES

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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

DATE: October 5, 2021

TO: Michael M. Gottesman, M.D.
Deputy Director for Intramural Research, NIH

FROM: Director
Division of Compliance Oversight, OLAW

SUBJECT: Animal Welfare Investigation (NIDA 21-21) – Animal Welfare Assurance A4149-01
[Case 15M]

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your September 28, 2021 memo regarding an incident of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the National Institute on Drug Abuse (NIDA). Your memo supplemented information in the preliminary email report from OACU on August 13, 2021. According to the information provided, OLAW understands that on the week of July 19, 2021, three rhesus macaques failed to receive their minimum, protocol-required daily water intake of 20 ml/kg. This occurred 2-3 times per week prior to the P.I. discovering the issue on August 10th and self-reporting the issue. It was subsequently determined that the protocol was also not followed regarding the gradual decrease, and then gradual increase, of the water rations. None of the animals appeared to be in ill-health or showed signs of dehydration. It was determined that the protocol deviations were likely caused by both miscommunication among laboratory/animal care staff and faulty record keeping.

Corrective and preventive actions included: revising the protocol to increase clarity; improve, and increase, water intake recordkeeping; adding end-of-day records checks of water bottle volume and fluid intake, and; more open and regular communication between all staff directly responsible for care and use of the animals. In addition, the ACUC added that the appropriate SOP must be referenced in the protocol and that the protocol must be checked for consistency with that SOP. Also, the PI and all listed personnel on the protocol will be required to re-attest to their awareness of their responsibilities, as described in both the SOP and the protocol.

The actions taken to resolve the issues and prevent recurrence were appropriate and accepted by OLAW. We appreciate being informed of this matter and find no cause for further action by this office.

Sincerely,

Brent C. Morse -S

Digitally signed by Brent C.
Morse -S
Date: 2021.10.05 14:37:00 -04'00'

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

cc: Dr. Stephen Denny
Dr. Richard Wyatt
Alexander F. Hoffman, Ph.D., Chair, NIDA ACUC



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

www.nih.gov

September 28, 2021

TO: Brent C. Morse, D.V.M.
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare

FROM: Deputy Director for Intramural Research, NIH

SUBJECT: Animal Welfare Investigations - Assurance D16-00602 (NIDA 21-21)

This correspondence conveys the results of an animal incident investigation by the National Institute on Drug Abuse (NIDA) ACUC in accordance with Assurance D16-00602 and PHS Policy IV.F.3. The incident involved failure to follow the water control procedures outlined in an ACUC-approved animal study proposal involving three rhesus monkeys. No monkeys were injured in this incident.

The event was first reported to the NIH Office of Animal Care and Use by the NIDA ACUC Chair on August 13, 2021.

Please contact me or Dr. Stephen Denny, Director, Office of Animal Care and Use, if additional information or clarifications are required.

Michael M.
Gottesman -S
Michael M. Gottesman, M.D.

Digitally signed by
Michael M. Gottesman -S
Date: 2021.09.30
12:00:11 -04'00'

Attachment

cc: Dr. Wyatt
Dr. Hoffman
Dr. Denny



TO: Dr. Michael Gottesman, Deputy Director for Intramural Research
FROM: Alexander F. Hoffman, Chair, NIDA Animal Care and Use Committee
DATE: 9/27/2021
SUBJECT: Reportable incident on protocol non-compliance

The National Institute on Drug Abuse Intramural Research Program, in accordance with Assurance A4149-01 and PHS Policy IV.F.3., reports the following incident of protocol non-compliance involving the use of fluid regulation in non-human primates under a protocol entitled "Single unit recording during economic choice for drugs and attentional bias to drug cues." A summary of the incident, major findings, and proposed remedies are described below.

Summary of incident: On 8/13/2021, the P.I. notified the ACUC Chair and Animal Program Director via email of protocol non-compliance. The email stated that, beginning on the week of July 19, 3 rhesus macaques failed to receive their minimum required daily water intake of 20 ml/kg. The email stated that this occurred 2-3 times per week prior to the P.I. discovering the issue on 8/10. None of the animals appeared to be in ill-health or showed signs of dehydration. A detailed fluid restriction protocol necessary to achieve stable behavioral training was provided and approved on this ASP which stipulated that "animals will not go below 20 ml/kg/day of fluid." The ACUC Chair immediately communicated this concern to the NIH Office of Animal Care and Use, and appointed an ACUC subcommittee on 8/16/2021 to further investigate this incident.

(1) Findings of the subcommittee

The subcommittee presented its findings to the fully convened ACUC on 9/24/2021.

From their careful review of documentation as well as statements obtained from all individuals directly involved, the subcommittee found three specific violations of the procedures as established in the ASP protocol, described below:

- 1) *Failure to receive minimum water rations.* All three monkeys received less than the minimum daily water ration, as described in the ASP (i.e., 20 mL/kg/d), on some days within this period. Although records indicate that monkeys received as little as 11 mL/kg/d on individual days, the average daily water ration during this period was not less than 19.5 mL/kg/d for any monkey. At this level, it is unlikely that any clinical signs/symptoms would be seen. Consistent with this, a veterinary evaluation of the

monkeys that was performed after discovery of the violation found them to be in good health, with no obvious differences from their prior physical exams.

- 2) *Procedure for graded water decrease was not followed.* The gradual decrease of fluids at the onset of water restriction, as described in the ASP (maximum decrease of 20 mL/kg/d), was not followed. Water availability was directly changed from ad libitum (~ 100 mL/kg/d) to 40 mL/kg/d in one day.
- 3) *Procedure of graded water increase was not followed.* In one instance, the gradual increase of fluids at the end of water restriction, as described in the ASP (maximum increase in 20 mL/kg/d), was not followed. Water availability was increased in one day from ~20 mL/kg/d to ad libitum. In this case, a surgical procedure was scheduled for the monkey, but the experimenter was not aware of this schedule until 2 days prior to surgery. This situation triggered an immediate return to ad libitum water availability, so the surgery could be performed on the scheduled date.

Based on these findings, it is clear that the failure to follow procedures described in the ASP represent a reportable animal welfare incident under OLAW Guidelines.

(2) Causes of Violations

From the information obtained by the committee, it was determined that the protocol deviations occurred with no explicit intent of wrongdoing nor any intent to jeopardize animal welfare. The mistakes were instead likely caused by both miscommunication among laboratory/animal care staff and faulty record keeping.

- 1) *Miscommunication.* Based on the written accounts from the two primary individuals involved in the day-to-day management of the protocol, and confirmed by the PI, communication between the supervisor and trainee was minimal. The supervisor stopped oversight of the trainee after about one week of training because of a perceived personality conflict. Throughout the period in question, little communication with the PI took place. Thus, there was a lack of effective communication between the trainee, supervisor, and PI. In addition, discussions with animal care staff revealed that the interactions between lab members and animal care staff were minimal.
- 2) *Faulty record keeping.* Both the trainee and supervisor kept separate records of water intake for the monkeys during behavioral training, and these two records did not always match. In the shared central lab spreadsheet, there was not a clear distinction between the calculated amount of supplemental water that needed to be given and the amount that was actually given. Importantly, there was also no record of the amounts of water ingested or given during the weekends, when animal care staff were in charge of providing water.

(3) Suggested Solutions

While the subcommittee recognized that this protocol violation did not result in harm to the animals, mitigation against future violations is paramount to ensuring both animal welfare and

research integrity. The subcommittee therefore proposed the following suggestions to prevent future issues:

- 1) *Protocol revision.* The current ASP contains a detailed description of the water restriction protocol. However, the ASP must be revised to include a description of the determination and recording of ad libitum water intake for each monkey, to get a clear baseline of unrestricted water intake. This determination should be done for a week prior to the start of restriction. Additionally, the ASP should indicate a clear schedule for progressive water restriction, once the baseline for each monkey has been determined. In addition, the current ASP states only that “Animals anesthetized for scheduled procedures will be removed from water regulation at least 24 hours prior to the procedure, in consultation with the animal program veterinarian.” Clearly, this timetable is at odds with the need to provide a gradual transition to ad libitum water (violation #3, above). This statement must be revised to state that “Animals anesthetized for scheduled, elective procedures will be removed from water regulation when sufficient time has been provided to allow for a gradual return to ad libitum water at least 24 hours prior to the procedure, in consultation with the animal program veterinarian.” The subcommittee also suggests that the ASP should include a provision that the facility veterinarian review the previous week’s water records with the PI/lab personnel prior to scheduling any elective surgical procedures, as an additional check of adequate fluid regulation.
- 2) *Improve accurate record keeping.* A written record of daily water intake for each monkey should be posted in the animal housing room, and this record should include weekend water intake. The data entered into laboratory records should exactly match the data entered into the housing room charts. To this end, the subcommittee noted that the facility veterinarian has recently implemented required, daily record keeping of water intake by animal care staff.
- 3) *Evening record checks.* It is suggested that the experimenter and supervisor carry out end-of-day checks (e.g., check water bottle fluid volume, review intake records, compare both together), which could be verified by personnel not in charge of the water restriction experiment.
- 4) *Open communication.* Effective, accurate, and regular communication between the trainee, supervisor, PI, and animal care staff is essential. The PI should have regular meetings with staff to gain feedback during water restriction experiments and should emphasize to all laboratory personnel that he must be *immediately* informed of any disagreements or perceived conflicts about supervision or procedures. The suggestions for record keeping and evening checks mentioned above should facilitate communication and information sharing. When animals are scheduled for elective surgery, the date and time of surgery should be indicated clearly (on cage card or on chart for example), so if a return to ad libitum water intake is necessary, it can be started with plenty of time prior to surgery to facilitate a gradual increase in water availability.

(4) ACUC consideration of the subcommittee report

At the ACUC meeting on 9/24/2021, the members voted unanimously to accept the subcommittee report and recommendations, with the following additional requirements. First, the ASP must directly reference Section 14 (Food or Water Regulation) of the NIDA IRP Rhesus SOP, and

language throughout the ASP must be checked for consistency with that SOP. Second, following revisions to the ASP as described above, the PI and all listed personnel on the protocol will be required to re-attest to their awareness of their responsibilities, as described in both the SOP and the ASP. A copy of this attestation will be kept on file with the ACUC administrator.

Concluding statement

The subcommittee found that a reportable animal welfare incident involving failure to adhere to the protocol did occur. Failure to both maintain proper communication/supervision, as well as a failure to maintain a more thorough documentation of water restriction records, contributed to this incident. Although the animals were not harmed by this protocol violation, the issues need to be carefully addressed by the PI in order to mitigate against any future violations of the ASP, or potential impacts on animal welfare. The PI duly reported this incident as soon as it was brought to their attention, and a recent post approval verification (PAV) visit of this laboratory that occurred prior to this incident (documented at the May 2021 ACUC meeting) did not reveal any specific concerns with this ASP. The subcommittee and ACUC therefore believe this failure of protocol compliance is likely to have been an isolated incident. With proper modifications to the protocol as described above, as well as improvements in both record keeping and communication that are actively being established among the PI, research, and animal care staff, the ACUC feels that such deviations are unlikely to occur in the future.

The NIDA IRP ACUC is committed to the highest animal welfare standards, and appreciates the support of OLAW in this regard. Should you have any additional questions or concerns regarding this report, please do not hesitate to contact me.

Sincerely,

(b) (6)

Alex Hoffman, Ph.D.

Chair

NIDA IRP Animal Care and Use Committee

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Friday, October 1, 2021 7:48 AM
To: Denny, Stephen (NIH/OD) [E]
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: D16-00602 NIH Animal Incident Report (NIDA 21-21)

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

Axel Wolff

From: Denny, Stephen (NIH/OD) [E] <stephen.denny@nih.gov>
Sent: Thursday, September 30, 2021 12:45 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: D16-00602 NIH Animal Incident Report (NIDA 21-21)

Dear OLAW/DCO,

The attached reports from the NIH Institutional Official and the National Institute for Drug Abuse (NIDA) ACUC address an animal incident involving the failure to comply with water regulation procedures listed in an ACUC-approved animal study proposal (ASP). No injuries were identified in the three rhesus monkeys assigned to this ASP.

The event was first reported to the NIH Office of Animal Care and Use by the NIDA ACUC Chairperson on August 13, 2021.

If you have any questions please contact me via email or at the phone number listed below. Thank you, Steve

STEPHEN DENNY, DVM, MS, DACLAM, DACVPM | Director, Office of Animal Care and Use | NIH Bethesda Campus, Building 31/Room B1C37 |
Phone: (301) 435-2188 | **NIH . . . Turning Discovery Into Health** |

Wolff, Axel (NIH/OD) [E]

A4149-15M

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Monday, August 16, 2021 7:11 AM
To: Denny, Stephen (NIH/OD) [E]
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: D16-0062 NIH Initial Animal Incident Report

Thank you for this preliminary report, Dr. Denny. We will start a new case file.
Axel Wolff

From: Denny, Stephen (NIH/OD) [E] <stephen.denny@nih.gov>
Sent: Friday, August 13, 2021 2:35 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: D16-0062 NIH Initial Animal Incident Report

OLAW-DCO, Good afternoon,

Today, the National Institute on Drug Abuse (NIDA) ACUC Chair notified this office of a principal investigator self-reporting their research team's failure to comply with an element of their ACUC-approved animal study protocol involving three rhesus monkeys on a behavior study. The involved monkeys are reported to be in good health.

The NIDA ACUC is conducting a full investigation. In the near future and following the investigation, the committee will propose corrective actions and render a report.

Feel free to contact me if you have any questions on this incident. Sincerely, Steve

STEPHEN L DENNY, DVM, MS, DACLAM, DACVPM | Director, Office of Animal Care and Use | National Institutes of Health | Building 31/Rm. B1C37, 9000 Rockville Pike, Bethesda, MD 20982 | Phone: (301) 435-2188 | <http://oacu.od.nih.gov> | NIH . . . *Turning Discovery Into Health*

