



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

June 9, 2021

Re: Animal Welfare Assurance  
A3377-01 [OLAW Case 8K]

Dr. David P. Norton  
Vice President for Research  
University of Florida  
(b) (4) Grinter Hall  
Gainesville, FL 32611-5500

Dear Dr. Norton,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your June 1, 2021 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the University of Florida, following up on an initial report on April 8, 2021. According to the information provided, OLAW understands that six rats were subjected to abdominal paracentesis to drain fluid, however this activity had not been described in the protocol, the procedure was performed by the laboratory staff, and it had not been reported to the veterinarians. The experimental drug in this study was not pharmaceutical grade, had been given intraperitoneally, and some rats experienced adverse effects such as dragging their hind limbs and becoming hunched. A pharmaceutical grade formulation of the drug was subsequently obtained but the pH was very low which probably caused the adverse reactions.

The corrective actions consisted of having a veterinarian observe the rats and requiring euthanasia of one showing adverse clinical signs. The experimental drug was buffered and the protocol was amended to reflect this. The Principal Investigator was directed to submit a corrective action plan to the Institutional Animal Care and Use Committee (IACUC) describing onboarding of new staff, ongoing training, and promptly reporting adverse animal events to the veterinary staff and IACUC. The laboratory staff was directed to undertake online retraining and the laboratory was placed under enhanced post-approval monitoring.

Based on its assessment of this explanation, OLAW understands that measures have been implemented to correct and prevent recurrence of this problem. OLAW concurs with the actions taken by the IACUC to comply with the PHS Policy.

Sincerely,

(b) (6)

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

cc: IACUC Chair



**Office of the Vice President for Research**

223 Grinter Hall  
PO Box 115500  
Gainesville, FL 32611-5500  
352-392-1582  
352-392-9605 Fax

June 1, 2021

Axel Wolff, 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

Dear Dr. Wolff:

The University of Florida, in accordance with Assurance D16-00244 (A3377-01) and PHS Policy IV.F.3., provides this report of a noncompliance in rats regarding unapproved procedures performed, animals past endpoint, failure to report animal health concerns to the ACS vets/IACUC. A preliminary report was sent on April 8, 2021 by IACUC Chair Daniel R. Brown.

On March 26, 2021 an anonymous report was submitted to the IACUC. In October 2020 rats had been placed on a long term doxorubicin dosing protocol. On October 23, 2020 a UF Animal Care Services (ACS) veterinarian recommended euthanasia for one rat found to be lethargic, dehydrated, thin, hunched, hypothermic, hyper salivating, with abnormal respirations. Study staff performed a necropsy on this animal and found red/brown abdominal fluid. Out of concerns for the remaining rats, between October 24-October 26, 2020 the lab staff performed an abdominal paracentesis procedure on an undocumented number (approximately 6) of rats, based on a protocol on the ACS website. Approximately 20-30 ml of fluid was drained from the abdomen of each of the rats. This procedure was not on the approved IACUC protocol and veterinary staff were not consulted before the procedure was performed by lab staff. On November 2, 2020 the laboratory staff consulted with an ACS veterinarian regarding abdominal paracentesis and whether it was appropriate to perform in this situation. The ACS veterinarian recommend abdominal paracentesis not be performed, and the ACS vet was not informed by lab staff that the procedure had already been performed. The doxorubicin used in these animals was non-pharmaceutical grade purchased from Sigma. As part of a non-survival surgery procedure on a different doxorubicin experiment, paracentesis was performed again in March 2021.

Between November 2020 and February 2021, 22 rats were injected IP with doxorubicin. Lab staff observed that the rats were hunched, squinty, laying prone/rotating to supine, and dragging the hind limbs in the hour following the injection. This behavior was not seen with prior cohorts, which alerted lab staff to possible problems. On February 11, 2021 an ACS veterinarian observed two rats the 1-2 hours after the injection, no concerns were noted. On February 15, 2021 an ACS veterinarian observed a rat during the injection and shortly following the injection

Report of non-compliance  
June 1, 2021  
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did observe the concerns lab staff had noticed previously (hunched, squinty, and laying prone/rotating to supine, dragging of the hind limbs). The lab had self-corrected to using a pharmaceutical grade doxorubicin with these animals but after further investigation it was noticed that the doxorubicin being used had a pH of 3 which likely caused the severe adverse effects seen in some of the animals (earlier studies had used doxorubicin at a higher pH). The laboratory is now buffering the doxorubicin with 1N potassium hydroxide.

The IACUC full committee voted on May 18, 2021 that this series of incidents constitutes noncompliance and has required the following corrective actions:

1. Within 2 weeks, the PI must submit a plan to the IACUC describing how compliance will be maintained within the laboratory. This plan should include onboarding of new staff, continuing education, and communication of adverse events to vet staff and the IACUC.
2. Post Approval Monitoring (PAM) with IACUC staff must occur during the next cohort of animals undergoing doxorubicin dosing. A follow-up PAM must occur 3 months following the initial PAM.
3. Within 2 weeks, all personnel listed on the protocol must take/retake the following AALAS Learning Library Course: a. Common Compliance Issues
4. Within 2 weeks, the PI must submit a protocol modification to add the 1N potassium hydroxide used to buffer the doxorubicin to the protocol.

The animals involved in this noncompliance are funded by the following grants:

- National Institutes of Health-R01HL144858-*Doxorubicin cardiotoxicity and the productive effects of exercise*
- National Institutes of Health-R01HL146443-*Doxorubicin-induced respiratory dysfunction and the protective effects of exercise*

The NIH funding components have been notified of the noncompliance.

The University of Florida is committed to protecting the welfare of animals used in research and appreciates the guidance and assistance provided by OLAW in this regard. Should you have any questions regarding this report, please contact Daniel R. Brown, Ph.D., IACUC Chair.

Thank you for your consideration of this matter.

Sincerely,

(b) (6)

David Norton, Ph.D.  
Vice President for Research  
Institutional Official

mpm

gw

## Wolff, Axel (NIH/OD) [E]

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**From:** OLAW Division of Compliance Oversight (NIH/OD)  
**Sent:** Wednesday, June 9, 2021 7:16 AM  
**To:** Research - IACUC  
**Cc:** OLAW Division of Compliance Oversight (NIH/OD)  
**Subject:** RE: Reportable noncompliance (2021Apr03) [ ref:\_00D412ElGo.\_5001K11ISao:ref ]

Thank you for this revised report, (b) (6) I'll substitute it and we'll respond soon.  
Axel Wolff

**From:** Research - IACUC <iacuc-crm@research.ufl.edu>  
**Sent:** Monday, June 7, 2021 10:47 AM  
**To:** OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>  
**Cc:** drbrown@ufl.edu; (b) (6)  
**Subject:** RE: Reportable noncompliance (2021Apr03) [ ref:\_00D412ElGo.\_5001K11ISao:ref ]

Good morning Dr. Wolff

Please see attached corrected report.

(b) (6)

----- Original Message -----

**From:** OLAW Division of Compliance Oversight [olawdco@od.nih.gov]  
**Sent:** 6/1/2021, 11:55 AM  
**To:** iacuc-crm@research.ufl.edu  
**Subject:** RE: Reportable noncompliance (2021Apr03) [ ref:\_00D412ElGo.\_5001K11ISao:ref ]

[External Email]  
[External Email]

Ok, thanks (b) (6) I'll wait for the revised version and substitute it.

Axel Wolff

**From:** Research - IACUC <iacuc-crm@research.ufl.edu>  
**Sent:** Tuesday, June 1, 2021 11:47 AM  
**To:** OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>  
**Cc:** (b) (6) drbrown@ufl.edu  
**Subject:** RE: Reportable noncompliance (2021Apr03) [ ref:\_00D412ElGo.\_5001K11ISao:ref ]

Hi Dr. Wolff

I apologize as there is an error in the first paragraph of the attached document. It should read:

The University of Florida, in accordance with Assurance D16-00244 (A3377-01) and PHS Policy IV.F.3., provides this report of a noncompliance in rats regarding unapproved procedures performed, animals past endpoint, failure to report animal health concerns to the ACS vets/IACUC. A preliminary report was sent on April 8, 2021 by IACUC Chair Daniel R. Brown.

I have sent a new report to the IO for signature and will resend.

Thank you

(b) (6)



----- Original Message -----

**From:** OLAW Division of Compliance Oversight [olawdco@od.nih.gov]  
**Sent:** 6/1/2021, 9:57 AM  
**To:** iacuc-crm@research.ufl.edu  
**Cc:** olawdco@od.nih.gov  
**Subject:** RE: Reportable noncompliance (2021Apr03) [ ref:\_00D412ElGo.\_5001K11ISao:ref ]

[External Email]

[External Email]

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

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

Deputy Director, OLAW

**From:** Research - IACUC <iacuc-crm@research.ufl.edu>

**Sent:** Tuesday, June 1, 2021 9:37 AM

**To:** OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>

**Cc:** drbrown@ufl.edu; mmahoney@ufl.edu; Moyal, Allison (NIH/NIDA) [E] <moyala@mail.nih.gov>; Desvigne-Nickens, Patrice (NIH/NHLBI) [E] <desvignp@nhlbi.nih.gov>; Kennedy, Laurel (NIH/NHLBI) [E] <laurel.kennedy@nih.gov>; Natarajan, Aruna (NIH/NHLBI) [E] <aruna.natarajan@nih.gov>

**Subject:** Reportable noncompliance (2021Apr03) [ ref: \_00D412ElGo.\_5001K11ISao:ref ]

To All Concerned,

Please see the attached report of a noncompliance from the University of Florida (D16-00244). A preliminary report was sent on April 8, 2021 by Dr. Daniel R. Brown.

The protocols involved in this noncompliance are funded by the NIH and the applicable program official and grants management specialist are cc'd on this email.

Please acknowledge receipt and let me know if you have any questions.

(b) (6)



**Wolff, Axel (NIH/OD) [E]**

A3377-8K

**From:** OLAW Division of Compliance Oversight (NIH/OD)  
**Sent:** Friday, April 9, 2021 7:45 AM  
**To:** Brown, Daniel R  
**Cc:** OLAW Division of Compliance Oversight (NIH/OD)  
**Subject:** RE: Potential IACUC Non-Compliance

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

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**From:** Brown, Daniel R <drbrown@ufl.edu>  
**Sent:** Thursday, April 8, 2021 10:50 AM  
**To:** OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>  
**Cc:** [REDACTED] (b) (6)  
**Subject:** Potential IACUC Non-Compliance  
**Importance:** High

To All Concerned,

This is preliminary report of a situation potentially involving failure to adhere to IACUC-approved protocols; participation in animal-related activities by individuals who have not been determined by the IACUC to be appropriately qualified and trained; and, adverse effects of treatments not reported to the IACUC at the University of Florida (Assurance #D16-00244). Briefly, it was alleged by a former study staff member that a number of irregularities have occurred during conduct of IACUC-approved (UF protocols #201910712, 201910797, and 201910975) rat cardiac dysfunction studies funded by NIH.

On 04/06/2021 I directed IACUC staff to initiate an investigation. A final report to our IACUC is expected within 30 days.

Please contact me with any questions or concerns.

Dan Brown



Daniel R. Brown, PhD  
Chairman, UF Institutional Animal Care and Use Committee  
Associate Professor of Infectious Diseases & Immunology  
College of Veterinary Medicine  
University of Florida  
Gainesville FL 32611-0880 USA  
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