



DEPARTMENT OF HEALTH & HUMAN SERVICES

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NATIONAL INSTITUTES OF HEALTH

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Office of Laboratory Animal Welfare
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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) 402-7065

August 7, 2019

Re: Animal Welfare Assurance
#A3245-01 (OLAW Case 3R]

Dr. Melur K. Ramasubramanian
Vice President for Research
Professor, Mechanical Engineering
University of Virginia
Box 400301
Charlottesville VA 22904-4301

Dear Dr. Ramasubramanian,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your August 1, 2019 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the University of Virginia, following up on an initial report on May 28, 2019. According to the information provided, OLAW understands that four mice on a cancer study were injected with an isotope not listed on the approved protocol and PET imaging was conducted which also had not been approved. The vivarium supervisor had not been notified about radioactive animals being placed in the containment cubicle, the radioactive warning signs did not have enough information, and the husbandry staff had not been briefed on the specific procedures to follow with the mice. Monitoring of tumor growth was conducted in an unauthorized area, cages were not appropriately labeled as biohazardous, and three of the mice died under gas anesthesia during imaging.

The corrective actions consisted of the Institutional Animal Care and Use Committee (IACUC) directing the Principal Investigator (PI) to stop further experiments and to euthanize the remainder of the animals. The PI was counseled, the protocol was amended, the PI will communicate with the Molecular Imaging Core staff and vivarium staff before starting a new study, training flow charts were developed, animal care staff was retrained, and the laboratory staff was counseled. The PI of the Core amended the protocol to include the isotope, the isoflurane vaporizer was replaced, the protocol template was revised to include husbandry staff caring for radioactive animals, communication was enhanced, Core staff will ensure animals are in clean and properly labeled cages before returning to the vivarium, protocols will be available to Core staff, a working group of key staff was established, and radioactive cage labeling was improved and the standard operating procedure was revised to reflect this.

Based on its assessment of this explanation, OLAW understands that measures have been implemented to correct and prevent recurrence of these problems. OLAW concurs with the actions taken by the IACUC to comply with the PHS Policy. Note that in response to your request, we have deleted preliminary report 2019-F. Thank you for keeping OLAW apprised on this matter.

Page 2 – Dr. Ramasubramanian
August 7, 2019
OLAW Case A3245-3R

Sincerely,

(b) (6)

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

cc: IACUC Chair
Director, Office of Animal Welfare

UNIVERSITY OF VIRGINIA
ANIMAL WELFARE COMPLIANCE REPORT

PHS Assurance # A3245-01

A preliminary email notification was sent to Dr. Brent Morse of OLAW by Angela Gamble, Director of the Office of Animal Welfare. It was understood that a full report would follow IACUC investigation. This document is a summary of the incident, actions taken, and final resolution.

UVA Compliance Case #: 2019-A (PI)
 2019-B (PI – Molecular Imaging Core Facility)

Nature of Incident(s):	Failure to adhere to approved protocol resulting in unapproved experiment (mice)
Summary of Incident:	<p>Four animals were injected with human cancer cells as per protocol. After several weeks, the animals were injected with a radioisotope and PET imaged daily by the Molecular Imaging Core for seven days. Animals were anesthetized with isoflurane for imaging as per the Core protocol by Core animal handlers. Both the PI and Core Facility PI were authorized by Radiation Safety to handle the radioisotope, but the particular isotope injected into the animals was not included in the approved animal use protocols for either the PI or the PI of the Core Facility. The PI also did not have approval for daily PET imaging in the animal use protocol. The Core Facility did not verify that that the PET imaging was in the PI's protocol prior to performing the PET imaging.</p> <p>The PI and Core Facility PI failed to properly notify the vivarium supervisor in advance of the radioactive animals being placed into the radioactive-dedicated housing cubicle within the vivarium. Radioactive signs were posted but were did not contain adequate information. The mechanisms for husbandry during the cool down period had not been established with the husbandry staff for the particular isotope used. It was unclear if the radioactive cages were adequately shielded.</p> <p>The PI's animal handler continued to monitor tumor growth as per protocol and IACUC policy; however, the monitoring occurred in an unauthorized animal transfer station within the radioactive area and proper biohazard cage labeling was not used.</p> <p>The Core Facility PI indicated that two animals died while under isoflurane anesthesia on the first day of imaging and a third died on day four of imaging. The Attending Veterinarian</p>

	believes the animals died under anesthesia and the deaths were not due to the isotope administration.
Action taken by IACUC:	<p>Upon discovery, the PI and Core Facility PI were told to discontinue the PET imaging and additional experiments involving the “new” isotope were not permitted. The PI euthanized the remaining animal and other tumor bearing animals slated for subsequent PET imaging. The Attending Veterinarian, PI, Core Facility PI, Core Facility animal handler, and Compliance Director met to discuss the issues. The Radiation Safety Manager was also consulted.</p> <p>At the next convened meeting, the IACUC discussed the incident and determined that the incident was a significant deficiency due to the protocol deviation. The PI and the PI of the Molecular Imaging Core received letters from the IACUC regarding their concerns and required a written corrective action plan.</p>
Action taken by PI:	<p>The PI provided a written corrective action plan to improve training and compliance. The PI submitted a modification to the protocol to include the radioisotope and PET imaging. Prior to each study, the PI will review the imaging plan with the members of the Molecular Imaging Core as well as the day before the start of an experiment to ensure that communication has been completed with both the Core Facility and vivarium staff. He will contact the vivarium supervisor prior to the start of experiments. He created training flow charts and retrained his animal handlers to ensure compliance when working with biohazards and radioisotopes. He also reviewed the information during two group meetings with his staff. He indicated that he will also follow the recommendations and requirements of the newly established working sub-committee referenced below by the Core PI.</p>
Action taken by Core PI:	<p>The PI of the Molecular Imaging Core provided a written corrective action plan. The PI submitted a modification to the protocol to include the radioisotope. The isoflurane vaporizer was retested and failed. It was replaced with a validated vaporizer. The IACUC protocol template was updated to reflect current practices where in vivarium staff perform husbandry duties for radioactive animals. He will increase his communication with collaborators using the Core as well as with the vivarium staff. Core staff will ensure that animals are placed into clean cages before being returned to the vivarium after radioisotope injection and will ensure that the cages are properly labeled. The Core Facility has a mechanism to view collaborating protocols wishing to use the facility.</p> <p>The PI established a working group including the Attending Veterinarian, Radiation Safety Officer, Compliance Director, IACUC member, and IACUC programmer. The labeling system for radioactive animal caging was improved and the</p>

	Attending Veterinarian updated their husbandry SOPs to reflect the change. The working group will continue to find methods for improvement in the protocol system as needed.
Action taken by IACUC:	The protocols were approved as modified. The IACUC felt that the PI and Core PI responded appropriately and no further action was deemed necessary.
Decision/Resolution:	The IACUC considered the incident resolved.
Federal Funding:	R01CA223767-01
Notification of Final Disposition:	<input checked="" type="checkbox"/> IO <input checked="" type="checkbox"/> OLAW <input type="checkbox"/> AAALAC

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Friday, August 2, 2019 6:32 AM
To: (b) (6)
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: UVA OLAW Compliance Report

Thank you for these reports, (b) (6) We will send responses soon.
Axel Wolff

From: (b) (6)
Sent: Thursday, August 1, 2019 2:35 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>; Wolff, Axel (NIH/OD) [E] <wolffa@od.nih.gov>
Cc: Ward, Joan (NIH/OD) [E] <wardjoa@od.nih.gov>; (b) (6) Ramasubramanian, Melur K (mkr5a) <mkr5a@virginia.edu>; Gamble, Angela (adr8s) <adr8s@virginia.edu>
Subject: UVA OLAW Compliance Report

Dr. Axel Wolff, Director of Compliance Oversight Office of Laboratory Animal Welfare National Institutes of Health RKL 1, Suite 360, MSC 7982
6705 Rockledge Dr., Bethesda, MD

Dr. Wolff:

I attach two compliance reports from our IACUC.

In these cases, the IACUC has investigated thoroughly, taken appropriate action and the committee has determined that these matters have been resolved to their satisfaction.

I have reviewed the reports and I concur with the committee responses and final determinations.

We made a preliminary report for our compliance item 2019-F. After further investigation we have determined that the animals and research involved were funded by neither NIH or NSF. A final report was sent to me as the IO but we are not submitting the final report to OLAW. We will, of course, forward that report if you wish.

Best regards,

(b) (6)

For Melur K. Ramasubramanian

(b) (6)

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Wednesday, May 29, 2019 6:45 AM
To: Gamble, Angela (adr8s)
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: preliminary notification - UVA (Assurance A3245-01): 2019-A, 2019-D, 2019-F, and 2019-H

Thank you for these preliminary reports, Ms. Gamble. We will start new case files and look forward to receiving the final reports from the IO after the IACUC has completed its investigation.

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

From: Gamble, Angela (adr8s) <adr8s@virginia.edu>
Sent: Tuesday, May 28, 2019 2:43 PM
To: Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov>; OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Gamble, Angela (adr8s) <adr8s@virginia.edu>; (b) (6)
Subject: preliminary notification - UVA (Assurance A3245-01): 2019-A, 2019-D, 2019-F, and 2019-H

Dear Dr. Morse,

This is to provide preliminary notification that the University of Virginia IACUC (PHS Assurance #A3245-01) has identified three potential significant deficiencies as a result of the recent semi-annual inspection and one significant deficiency independent of the inspection. Each item below is under investigation and review by the IACUC. We are working with the PIs towards resolution and will send you a complete report for each incident once it has been resolved. The items are listed by IACUC Tracking Number.

- 2019-A: Conducting an animal related activity without appropriate IACUC review and approval (mice)
- 2019-D: Use of an expired anesthetic and use of an inappropriate method of euthanasia (mice)
- 2019-F: Condition that *potentially* jeopardized the health or well-being of animals resulting in the *potential* for harm or death (neonatal mice)
- 2019-H: Condition that jeopardized the well-being of animals resulting in actual death (neonatal mice)

Should you have any questions or concerns prior to receiving our final reports, please do not hesitate to contact me.

Sincerely,
 Angela Gamble

Angela Gamble
 University of Virginia
 Director, Office of Animal Welfare
 Charlottesville, VA 22908
 PH: (b) (6)