



USDA-APHIS-Animal Care



ANIMAL WELFARE COMPLAINT			
Complaint No. AC19-481	Date Entered: 10-Jul-19	Processed By: SSE	
Referred To: FRANK/GARLAND		Reply Due: 11-Aug-19	
Facility or Person Complaint Filed Against			
Name: UNIVERSITY OF CALIFORNIA- DAVIS		Customer No.: 9192	License No.: 93-R-0433
Address: ONE SHIELDS AVE		Email Address:	
City: DAVIS	State: CA	Phone No.:	
Complainant Information			
Name: (b) (6), (b) (7)(C), (b) (7)(D)		Organization:	
Address:		Email Address: (b) (6), (b) (7)(C), (b) (7)(D)	
City:	State:	Phone No.:	
How was the Complaint received? Email			
Details of Complaint: SEE ATTACHED			
Results: Animal Care inspectors conduct unannounced inspections for all USDA registered and licensed facilities. Our authority is to ensure that they meet the standards required by Federal regulations. We also perform inspections in response to valid concerns and complaints received from the public to ensure the well-being of the animals and compliance with Federal law. The specific issues in this complaint was addressed during a previous inspection. When non-compliant items are found, these non-compliances are cited on the inspection report under the most accurate regulation based on the circumstances of the issue. Multiple non-compliances for the same issue are only cited when appropriate. With the exception of focused inspections, our inspectors evaluate the facility for compliance with all applicable regulations. Although all regulatory requirements are assessed, only noncompliant items are listed on the inspection report. We will continue to inspect this facility to make sure that past non-compliances are corrected and that AWA-regulated animals are protected to the fullest extent of Federal law.			
Application Kit Provided: Yes: <input type="checkbox"/> No: <input checked="" type="checkbox"/>			
Inspector:		Date:	
Reviewed By: KATHLEEN GARLAND		Date: 07-July-2019	
Digitally signed by KATHLEEN GARLAND Date: 2019.07.10 13:00:05 -07'00'			



Animal and Plant
Health Inspection
Service

July 10, 2019

Animal Care
4700 River Road
Riverdale, MD 20737

(b) (6), (b) (7)(C), (b) (7)(D)

Dear Complainant,

Thank you for your correspondence dated 8-Jul-19. We are reviewing your concerns and assigned tracking number AC19-481. Please allow us enough time (30 to 60 days) to thoroughly look into your concerns. You may submit a request to the Animal and Plant Health Inspection Service (APHIS) Freedom of Information Act (FOIA) office to obtain any publically available information regarding our review.

FOIA Requests can be submitted three ways:

1. Web Request Form: <https://efoia-pal.usda.gov/App/Home.aspx>
2. Fax: 301-734-5941
3. US Mail:
USDA- APHIS- FOIA
4700 River Road, Unit 50
Riverdale, MD 20737

Should you have any questions regarding the APHIS FOIA process or need assistance using the Web Request Form **please contact the APHIS FOIA office at 301-851-4102.**

Animal Care is a program within the U.S. Department of Agriculture (USDA) that directs activities to ensure compliance with and enforcement of the Animal Welfare Act and the Horse Protection Act. Animal Care establishes standards of humane treatment for regulated animals and monitors and achieves compliance through inspections, enforcement, education, and cooperative efforts under the Acts.

Please be assured that we will look into your concern(s) and take appropriate action(s).

Thank you for your interest into the humane treatment of these animals.

Sincerely,

Betty Goldentyer
Associate Deputy Administrator
Animal Care



September 26, 2019

Animal and Plant
Health Inspection
Service

Animal Care
4700 River Road
Riverdale, MD
20737

(b) (6), (b) (7)(C), (b) (7)(D)

Dear Complainant:

Thank you for your correspondence dated 20-Sep-19. We are reviewing your concerns and assigned tracking number AC19-481. Please allow us enough time (30 to 60 days) to thoroughly look into your concerns. You may submit a request to the Animal and Plant Health Inspection Service (APHIS) Freedom of Information Act (FOIA) office to obtain any publically available information regarding our review.

FOIA requests can be submitted three ways:

1. Web Request Form: <https://efoia-pal.usda.gov/App/Home.aspx>
2. Fax: (301) 734-5941
3. U.S. Mail:
USDA-APHIS-FOIA
4700 River Road, Unit 50
Riverdale, MD 20737

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Please be assured that we will look into your concern(s) and take appropriate action(s).

Thank you for your interest into the humane treatment of these animals.

Sincerely,

Betty Goldentyer
Associate Deputy Administrator
Animal Care

From: (b) (6), (b) (7)(C), (b) (7)(D)
Sent: Monday, July 8, 2019 4:14 PM
To: Gibbens, Robert - APHIS
Cc: AC West
Subject: Official Complaint UC Davis

(b) (6), (b) (7)(C), (b) (7)(D)



Dr. Robert Gibbens
7/8/19
Director, Western Region
USDA/APHIS/AC
2150 Center Ave.
Building B, Mailstop 3W11
Fort Collins, CO 80526-8117

Dr. Gibbens,

I am contacting you today to file an Official Complaint against the University of California, Davis (93-R-0433) for the illnesses of 54 Titi monkeys, including the deaths of 3 of those animals.

This situation was caused by use of a new version of a vaccine, which had previously not been used in Titi monkeys. It is very clear that the monkeys became symptomatic as a result of this vaccine, resulting in very serious illnesses. The use of this vaccine which was had not previously been used in Titi monkeys (the manufacturer disclosed that the vaccine is now grown on a different cell type than previous vaccines) should have been initially tried in a smaller group of primates instead of a cohort of 64. Over 80% of the monkeys developed clinical signs, again leading to 3 deaths. This incident was a clear violation of either Sec. 2.38 Misc. (f)(1) Animal Handling or Sec. 2.33 Attending Veterinarian and Adequate Veterinary Care. (see attached document)

Obviously, the fact that this vaccine had been used in macaque monkeys is irrelevant. These are two very dissimilar species of primates.

As you know, seven infant primates died during 2018, following tattooing. This incident was also a clear violation of either Sec. 2.38 Misc. (f)(1) Animal Handling or Sec. 2.33 Attending Veterinarian and Adequate Veterinary Care. (see attached document)

As you also know, the University of California, Davis, recently paid a \$5000 fine for the death of a rabbit, which was cited in an inspection from July of 2016.

As you know, this facility has racked up six more citations in the period since July of 2016, including three critical citations. Collectively, these citations have accounted for the deaths of a guinea pig and a rabbit, and injuries to two primates (i.e. for details see our September 2018 Official Complaint posted at: <https://saenonline.org/news-media-news-2018/University-of-California-Davis-Official-Complaint-8-4-18.pdf>).

Now it has come to light that seven infant macaque monkeys have died, three Titi monkeys have died, and over 50 more Titi monkeys were made seriously ill. It is long past time for the University of California, Davis, to be severely penalized by the USDA. Otherwise, your office should give up the pretense of enforcing the Animal Welfare Act, because if UC Davis is not severely punished for this many deaths and illnesses, then this law is meaningless.

I must insist that your office immediately open a full investigation of these incidents, and the previous deaths/injuries, and at the completion of your probe, levy the maximum fine allowable under the Animal Welfare Act of \$10,000 per infraction/per animal. This should result in a penalty of over \$600,000.

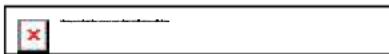
It is eminently clear that the University of California, Davis believes that it is above the law, and routinely flaunts the authority of the USDA. It is time for your office to take meaningful action against this lawbreaking lab to show the administration that any further animal deaths will simply not be tolerated.

(b) (6), (b) (7)(C), (b) (7)(D)

Many major violations of the Animal Welfare Act have piled up at UC Davis, and these failures to comply with the federal law are often connected either to deaths or serious injuries. Because multiple animals have died as a result of University of California, Davis's long history of flagrant violations of the Animal Welfare Act, I must again insist that you take the most severe action allowable under the Animal Welfare Act and begin the process of issuing the maximum allowable fine of \$10,000 per infraction against University of California, Davis, at the completion of a new investigation.

I look forward to hearing from you in the near future about the fate of this facility.

Sincerely,



(b) (6), (b) (7)(C), (b) (7)(D)

(b) (6), (b) (7)(C), (b) (7)(D)

Attachments: 2 UC Davis Reports

UNIVERSITY OF CALIFORNIA, DAVIS

BERKELEY • DAVIS • IRVINE • LOS ANGELES • MERCED • RIVERSIDE • SAN DIEGO • SAN FRANCISCO



SANTA BARBARA • SANTA CRUZ

OFFICE OF RESEARCH

(b) (6), (b) (7)(C)

1850 RESEARCH PARK DRIVE
DAVIS, CALIFORNIA 95618

TELEPHONE: 530 754 7764
RESEARCH UCDAVIS.EDU

April 1, 2019

AXEL WOLFF, M.S., D.V.M.

Deputy Director
Office of Laboratory Animal Welfare
National Institutes of Health
RKL1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982

RE: Institutional Report - D16-00521 # (A3433-01)

**Follow-up to adverse effect report for 2018 Titi clinical cases of vaccine induced disease
CNPRC base grant number P51OD011107**

Dear Dr. Wolf:

In accordance with Assurance D16-00521 # (A3433-01) and PHS Policy IV.F.3., UC Davis is providing a comprehensive summary report of the 2018 vaccine induced disease that occurred in our Titi monkey colony. This situation was previously reported in September 2018 and discussed with you over the phone on multiple occasions with our (b) (6), (b) (7)(C). This incident was self-reported to USDA.

In August 2018 the CNPRC vaccinated 64 Titi monkeys with 0.25 ml of the Vanguard DM (canine distemper/measles) vaccine. Between 9-15 days post vaccination animals presented for lameness/polyarthritis, papular rash, and conjunctivitis. All affected animals (54) had dermatitis and of those, approximately 20 animals showed signs of lameness or reluctance to move. We collected skin biopsies that showed lesions consistent with viral infection such as morbillivirus (potentially measles or canine distemper). Three non-vaccinated animals presented with a mild rash that was consistent with the papular lesions seen on the infected animals. We suspected there was limited transmission of the vaccine virus.

A subset of animals became significantly compromised and the family groups were housed in quads to ensure easy access to food and water. The laboratory staff suspended all research activities during

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

April 1, 2019

Page 2

the illness. The lab staff hand fed compromised animals multiple times per day to help support them. Clinical laboratory abnormalities included profoundly elevated GGT (1000-3000) in a few animals, anemia in 2 animals, and severely elevated bilirubin in one animal. Ultimately 3 animals were euthanized due to clinical compromise related to the infection. Subsequent histopathology found the most significant damage to epithelium of the bile ducts and pancreas for 2 of the cases. One of the euthanized animals had clinical evidence of abnormal clotting and had developed a secondary bacterial pneumonia. All 3 cases had changes in the skin, kidneys, and gut.

The histopathology results for the biopsies and the first necropsy were rushed to aid in the management of the other affected animals. All animals showing signs of discomfort were provided analgesics at clinical discretion (meloxicam, buprenorphine, and or Simbadol). Animals appearing dehydrated were given supportive fluid therapy as needed. Once we learned of the pathologist's suspicion of a secondary bacterial pneumonia, the clinically compromised animals were also treated with a course of antibiotics.

This lot of measles vaccine had been used without issue in rhesus macaque infants concurrently. Historically we have used the same vaccine in Titi monkeys, but it is currently produced by a different manufacturer. Investigative conversations with the manufacturer revealed that the vaccine viruses are not grown on the same cell type and we suspect this may have contributed to genetic changes - making the vaccine no longer safe for use in Titis.

We have saved a sample of the vaccine from one of the lots used in these Titis and are interested in using PCR and sequencing to confirm if this disease was caused by the attenuated measles or distemper virus. We are also planning to serologically evaluate the Titis over time to confirm if any non-vaccinated animals seroconverted.

If you have any questions, please do not hesitate to contact our (b) (6), (b) (7)(C) or by email at (b) (6), (b) (7)(C)@ucdavis.edu.

Sincerely,

(b) (6), (b) (7)(C)

/pk

c: IACUC
AAALAC

UNIVERSITY OF CALIFORNIA, DAVIS

BERKELEY • DAVIS • IRVINE • LOS ANGELES • MERCED • RIVERSIDE • SAN DIEGO • SAN FRANCISCO



SANTA BARBARA • SANTA CRUZ

OFFICE OF RESEARCH

(b) (6), (b) (7)(C), (b) (7)(D)

1850 RESEARCH PARK DRIVE
DAVIS, CALIFORNIA 95618

TELEPHONE: 530.754.7764
RESEARCH@UCDAVIS.EDU

April 1, 2019

AXEL WOLFF, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare
National Institutes of Health
RKL1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982

RE: Institutional Report - D16-00521 # (A3433-01)
Follow-up to adverse effect report for 2018 Nyanzol-D dye marking
CNPRC Base Grant number P51OD011107

Dear Dr. Wolf:

In accordance with Assurance D16-00521 # (A3433-01) and PHS Policy IV.F.3., UC Davis is providing a comprehensive summary report of the 2018 infant macaque deaths following routine Nyanzol-D dye marking, as well as the results of infant dye marking practice changes currently in place. This adverse effect from the dye marking was previously reported in 2018 and discussed with you over the phone on multiple occasions with our (b) (6), (b) (7)(C), (b) (7)(D). This incident was self-reported to USDA. Below please find the comprehensive summary and practice changes that have been successfully implemented.

Background

The CNPRC has been using Nyanzol-D for dye marking animals since 2012. During this time the routine health surveillance round-ups were changed from three times a year to twice a year mirroring standard practice among the other National Primate Centers. Through this process it was determined that the current product used for dye marking at that time, Miss Clairol, was not providing enough coverage between the semi-annual round-ups. An alternative dye marking product was sought out. The Primate Center at Cayo Santiago in Puerto Rico was using Nyanzol-D for dye marking with successful coverage over multiple months. The CNPRC recipe was derived from the recipe used at

Cayo Santiago. Since use of Nyanzol-D began six years ago approximately 24,000 animals have been dye marked using this product.

Incidents

In March and April 2018 seven infants came in to the hospital for emergency care following completion of routine round up. The veterinary staff provided clinical assessment of two of the infants that were brought to the hospital for emergency care. Both infants presenting to the hospital had generalized weakness and respiratory distress. Dye was noted on the lips and tongues of two infants. Endotracheal intubation was attempted. Both infants had severe edema and swelling of the larynx and tongue, making intubation difficult. Emergency drugs were administered, which had minimal effect on the laryngeal swelling. Despite treatment attempts, clinical conditions of the infants did not improve, and humane euthanasia was elected. The other infants were either found dead or euthanized upon arrival at the hospital.

Pathology Results

A total of seven infants were submitted to necropsy for sudden death or respiratory distress within 24 hours of round up. On examination, all 7 had some amount of dye on the fur, skin, and/or around or inside the nose and mouth. 4 monkeys had throat or laryngeal edema, 3 had hyper-inflated lungs, 2 had a mixture of hyperinflation/inflation and heavy/wet lungs, and 1 had diffusely heavy wet lungs. All animals had normal GI contents. Preliminary histology data on the first 3 animals showed 1 animal had an acute bronchopneumonia, unrelated to round up procedures. To arrive at definitive diagnoses, all cases were evaluated by all of the pathologists and findings summarized.

Summary of Pathology results

All pathologists subsequently reviewed the gross findings and histology, which are summarized in the table below.

Anaphylaxis was conclusively diagnosed via histologic evidence of laryngeal/tracheal edema with variably lung pathology. One animal submitted on 3/21 is equivocal due to unavailability of the trachea/larynx for examination. One animal submitted on 4/4 is definitively NOT consistent with anaphylaxis, but rather a severe bacterial pneumonia.

Date	Location	Age	Sex	Gross	Dye	Histo	Anaphylaxis?
3/21/2018	NC10	1 day	F	Red, wet lungs. Hemorrhage over cerebellum. Milk in stomach, rest of GIT normal.	3+	Larynx/trachea not available. Lung-multifocal hemorrhage, neutrophils in alveoli. Brain-minimal hemorrhage.	Sepsis likely, anaphylaxis less likely

Date	Location	Age	Sex	Gross	Dye	Histo	Anaphylaxis?
3/21/2018	NC10	4 days	M	Lungs pink. Milk in stomach, rest of GIT empty	2+	Mild laryngeal and tracheal edema. Vacuolation in vessels of the lungs. Minimal hemorrhage in brain.	Probable
4/4/2018	NC13	16 days	M	Lungs mostly pink, some mottling of two lobes. Milk throughout GIT.	1+	Severe neutrophilic bronchopneumonia with bacteria	No
4/10/2018	NC14	3 days	M	Edema of larynx and subcutaneous tissues of neck. Arborizing red pattern in lungs. Milk throughout GIT.	3+	Laryngeal edema, tracheal edema. Hemorrhage and vasculitis in the lungs.	Yes
4/10/2018	NC14	19 days	M	Laryngeal edema, hyperinflated lungs. Hemorrhage over left temporal lobe. Milk throughout GIT.	1+	Laryngeal edema, tracheal edema. Mild perivascular edema and reactive endothelium in the lung.	Yes
4/10/2018	NC14	7 days	M	Caudal laryngeal edema. Hyperinflated lungs. Milk throughout GIT.	1+	Laryngeal edema, tracheal edema. Perivascular edema in liver and brain.	Yes
4/10/2018	NC 14	13 days	M	Laryngeal/facial, nasal cavity edema. Red arborizing pattern and hyperinflation of lungs. Milk throughout GIT.	3+	Laryngeal and tracheal edema. Minimal perivascular edema. Retinal hemorrhage. Possible neuronal injury in brain.	Yes

Review of procedures

There were no new procedures introduced into any of these round-ups. The processes were all the same and the dye lot being used had been in use for several months. The infants were not anesthetized, did not receive any vaccinations, had a physical exam, eye ointment was applied to help prevent dye from getting in the eyes, had a blood sample collected, received a tattoo, and then received a dye mark. Post-round-up animal technicians observed all animals until fully recovered from sedation, and performed additional checks through the afternoon.

The Nyanzol-D dye mark is used at the Oregon Primate Center, Tulane Primate Center, and at Cayo Santiago in Puerto Rico. The recipe the CNPRC uses calls for warm water, 3% hydrogen peroxide and a measured amount of dye powder. The dye powder is measured out in advance once a new shipment arrives. The measured amounts are placed in Ziploc bags and placed inside an empty container that previously contained the dye powder.

Historically the CNPRC has only applied a small dye mark on the infants back as an indicator that it has undergone a round-up. In recent years, investigators have been using north colony animals as part of their research studies. It is very common for young infants to venture away from their mothers and "play" and investigators requested individual dye marks on the infants in order to determine individual animals when performing observations. This process of dye marking infants at round-up had been going on for several years or more.

After these incidents the dye marks of the dams were listed out and one commonality was that most of the dams have arm dye marks which put the wet dye in close proximity to the dam's nipples.

Conclusions

The initial findings suggested that the infants had exposure to dye that was present on their dam. Although there hadn't been any official change in procedures, the general consensus was that prematurely placing a young infant on an anesthetized dam with a fresh dye mark could increase the opportunity for the infant to get dye on its face, nose and mouth. Subsequent finding supported this conclusion.

Plans Moving Forward

Moving forward the following guidelines to Nyanzol -D dye marking at the CNPRC were agreed upon:

- Infants 6 months and younger will not be dye marked. If there is a special request for dye marking infants < 6 months of age Miss Clairol will be used.
- Infants will be placed on a warming pad when temperatures are cool during round-up, or under the radiant heaters near the staff working the round-up table. All other animals will be placed a distance away from the table for recovery. The plan is that the dams will not look for their infants until they are mostly recovered and the infants who are not anesthetized will not be able to wander into other animals and hopefully minimize the risk of dye transfer onto the infants.
- All animals will have excess dye wiped off after application.

Semi-annual round-ups following the implementation of the steps noted above have since proceeded smoothly without issues involving infants and dye marking. These steps were incorporated into our standard practice.

If you have any questions, please do not hesitate to contact our IACUC Director at (b) (6) or by email at (b) (6), (b) (7)(C)@ucdavis.edu.

Sincerely,

(b) (6)

(b) (6), (b) (7)(C)

/pk

c: IACUC
AAALAC

From: (b) (6), (b) (7)(C), (b) (7)(D)
To: [Goldentyer, Betty J - APHIS](#)
Cc: aceast@aphis.usda.gov; [Benson, Amy V - APHIS](#)
Subject: Re: Official Request for UC-Davis Fine (Primate Deaths)
Date: Friday, September 20, 2019 5:14:14 PM
Attachments: [UC Davis 061319.pdf](#)

Hi (b) (6), (b) (7)(C), (b) (7)(D) never received an acknowledgement to this letter (although we did for another sent more recently on a different topic). May we receive a response? Thank you, (b) (6), (b) (7)(C), (b) (7)(D),
(b) (6), (b) (7)(C), (b) (7)(D)

On Thu, Jun 13, 2019 at 9:00 AM (b) (6), (b) (7)(C), (b) (7)(D) > wrote:

Dear Dr. Goldentyer, please see attached a letter from (b) (6), (b) (7)(C), (b) (7)(D) requesting a \$70,00 fine to UC-Davis for 7 accidental infant primate deaths. Thank you for your attention this matter, and for all that you do to help prevent animal cruelty.

Kind regards,

--

(b) (6), (b) (7)(C), (b) (7)(D)



--

(b) (6), (b) (7)(C), (b) (7)(D)



(b) (6), (b) (7)(C), (b) (7)(D)

June 13, 2019

Dr. Elizabeth Goldentyer
Regional Director, Eastern Region USDA/APHIS/Animal Care (AC)
920 Main Campus Drive, Suite 200
Raleigh, NC 27606-5210

Dear Dr. Goldentyer,

We are writing to file an Official Complaint against the University of California - Davis (93-R-0433) for severe and recent violations of the Animal Welfare Act which resulted in the painful and unnecessary poisoning deaths of 7 infant non-human primates in 2018.

As evidenced below in documents we obtained via the Freedom of Information Act these painful infant deaths were a result of staff negligence and failure to follow protocol. As you may know, this is at least the second time UC-Davis has done this; In 2005, UC-Davis was fined \$4,815 for killing 7 primates.¹

Infant Deaths

As documented in a recently revealed April 17, 2019 letter from Axel Wolff, Deputy Director, Office of Laboratory Animal Welfare to Dr. Prasat Mohapatra, Vice Chancellor for Research at the University of California-Davis, OLAW stated:

"...OLAW understands that seven infant macaques died suddenly after they and their mothers had been marked with dye for identification. ...The infants had face, nose, and mouth exposure to the dye which was present on the mother.

In an Institutional Report - D16-00521 # (A3433-01) dated April 1, 2019, UC-Davis detailed these deaths:

"seven infants came in to the hospital for emergency care.....Both infants presenting to the hospital had generalized weakness and respiratory distress. Dye was noted on the lips and tongues of two infants. ... Both infants had severe edema and swelling of the larynx and tongue, making intubation difficult...The other infants were either found dead or euthanized upon arrival at the hospital.

"A total of seven infants were submitted to necropsy ...On examination, all 7 had some amount of dye on the fur, skin, and/or around or inside the nose and mouth. 4 monkeys had throat or laryngeal edema, 3 had hyper-inflated lungs, 2 had a mixture of hyperinflation/inflation and heavy/wet lungs, and 1 had diffusely heavy wet lungs. ...1 animal had an acute bronchopneumonia, unrelated to round up procedures.

Request for \$70,000 Fine

(b) (6), (b) (7)(C), (b) (7)(D) hereby files an Official Complaint against the University of California - Davis (93-R-0433) for multiple serious violations of the Animal Welfare Act. We respectfully request your office conduct an immediate investigation into these abuses. Given that these abuses are not contested and UC-Davis has admitted these failures in signed documents, we request UC-Davis be fined a total of \$70,000, which reflects the maximum penalty of \$10,000 per infraction, per animal.

¹ APHIS Case Number: CA05004-AC, Nov. 24, 2005.

(b) (6), (b) (7)(C), (b) (7)(D)

A large black rectangular redaction box covering the signature area.

Thank you for your consideration of this request, and we look forward to hearing from you.

Sincerely,

(b) (6), (b) (7)(C), (b) (7)(D)

A large black rectangular redaction box covering the signature area.

Attachment: OLAW Report



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

April 17, 2019

Re: Animal Welfare Assurance
A3433-01 [OLAW Case 2L]

(b) (6), (b) (7)(C)

University of California, Davis
1850 Research Park Drive
Davis, California 95618

Dear (b) (6), (b) (7)(C)

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your April 1, 2019 letter reporting an adverse event involving nonhuman primates at the University of California- Davis, following up on an initial telephone report on April 24, 2018. According to the information provided, OLAW understands that seven infant macaques died suddenly after they and their mothers had been marked with dye for identification. A switch in dye product had been made because the original formulation faded between semiannual animal round ups. Previous marking of animals with the new product at several facilities had not caused any problems. The infants had face, nose, and mouth exposure to the dye which was present on the mother.

The immediate action taken upon discovery of the compromised infants consisted of providing emergency veterinary care. The treatments were unsuccessful and the animals were euthanized while others had been found dead. Necropsies were conducted and the findings pointed to anaphylaxis as the cause of death in five cases and sepsis in two. To prevent a recurrence, infants aged six months or younger will not be marked with dye, any infants that must be marked will be given the original formulation, heat sources will be used when processing animals in cool weather, anesthetized mothers and babies will be kept apart until recovered to minimize dye transfer, and excess dye will be wiped off. Standard operating procedures have been revised to reflect these changes and no further incidents have occurred.

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 institution to comply with the PHS Policy on Humane Care and Use of Laboratory Animals.

Sincerely,

(b) (6)

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

cc: IACUC Chair
Robert Gibbens, D.V.M., USDA-APHIS-AC

20-03433_000064

UNIVERSITY OF CALIFORNIA, DAVIS

BERKELEY • DAVIS • IRVINE • LOS ANGELES • MERCED • RIVERSIDE • SAN DIEGO • SAN FRANCISCO



SANTA BARBARA • SANTA CRUZ

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(b) (6), (b) (7)(C)

April 1, 2019

AXEL WOLFF, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare
National Institutes of Health
RKL1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982

RE: Institutional Report - D16-00521 # (A3433-01)
Follow-up to adverse effect report for 2018 Nyanzol-D dye marking
CNPRC Base Grant number P51OD011107

Dear Dr. Wolf:

In accordance with Assurance D16-00521 # (A3433-01) and PHS Policy IV.F.3., UC Davis is providing a comprehensive summary report of the 2018 infant macaque deaths following routine Nyanzol-D dye marking, as well as the results of infant dye marking practice changes currently in place. This adverse effect from the dye marking was previously reported in 2018 and discussed with you over the phone on multiple occasions with our (b) (6), (b) (7)(C). This incident was self-reported to USDA. Below please find the comprehensive summary and practice changes that have been successfully implemented.

Background

The CNPRC has been using Nyanzol-D for dye marking animals since 2012. During this time the routine health surveillance round-ups were changed from three times a year to twice a year mirroring standard practice among the other National Primate Centers. Through this process it was determined that the current product used for dye marking at that time, Miss Clairol, was not providing enough coverage between the semi-annual round-ups. An alternative dye marking product was sought out. The Primate Center at Cayo Santiago in Puerto Rico was using Nyanzol-D for dye marking with successful coverage over multiple months. The CNPRC recipe was derived from the recipe used at

Cayo Santiago. Since use of Nyanzol-D began six years ago approximately 24,000 animals have been dye marked using this product.

Incidents

In March and April 2018 seven infants came in to the hospital for emergency care following completion of routine round up. The veterinary staff provided clinical assessment of two of the infants that were brought to the hospital for emergency care. Both infants presenting to the hospital had generalized weakness and respiratory distress. Dye was noted on the lips and tongues of two infants. Endotracheal intubation was attempted. Both infants had severe edema and swelling of the larynx and tongue, making intubation difficult. Emergency drugs were administered, which had minimal effect on the laryngeal swelling. Despite treatment attempts, clinical conditions of the infants did not improve, and humane euthanasia was elected. The other infants were either found dead or euthanized upon arrival at the hospital.

Pathology Results

A total of seven infants were submitted to necropsy for sudden death or respiratory distress within 24 hours of round up. On examination, all 7 had some amount of dye on the fur, skin, and/or around or inside the nose and mouth. 4 monkeys had throat or laryngeal edema, 3 had hyper-inflated lungs, 2 had a mixture of hyperinflation/inflation and heavy/wet lungs, and 1 had diffusely heavy wet lungs. All animals had normal GI contents. Preliminary histology data on the first 3 animals showed 1 animal had an acute bronchopneumonia, unrelated to round up procedures. To arrive at definitive diagnoses, all cases were evaluated by all of the pathologists and findings summarized.

Summary of Pathology results

All pathologists subsequently reviewed the gross findings and histology, which are summarized in the table below.

Anaphylaxis was conclusively diagnosed via histologic evidence of laryngeal/tracheal edema with variably lung pathology. One animal submitted on 3/21 is equivocal due to unavailability of the trachea/larynx for examination. One animal submitted on 4/4 is definitively NOT consistent with anaphylaxis, but rather a severe bacterial pneumonia.

Date	Location	Age	Sex	Gross	Dye	Histo	Anaphylaxis?
3/21/2018	NC10	1 day	F	Red, wet lungs. Hemorrhage over cerebellum. Milk in stomach, rest of GIT normal.	3+	Larynx/trachea not available. Lung-multifocal hemorrhage, neutrophils in alveoli. Brain-minimal hemorrhage.	Sepsis likely, anaphylaxis less likely

Date	Location	Age	Sex	Gross	Dye	Histo	Anaphylaxis?
3/21/2018	NC10	4 days	M	Lungs pink. Milk in stomach, rest of GIT empty	2+	Mild laryngeal and tracheal edema. Vacuolation in vessels of the lungs. Minimal hemorrhage in brain.	Probable
4/4/2018	NC13	16 days	M	Lungs mostly pink, some mottling of two lobes. Milk throughout GIT.	1+	Severe neutrophilic bronchopneumonia with bacteria	No
4/10/2018	NC14	3 days	M	Edema of larynx and subcutaneous tissues of neck. Arborizing red pattern in lungs. Milk throughout GIT.	3+	Laryngeal edema, tracheal edema. Hemorrhage and vasculitis in the lungs.	Yes
4/10/2018	NC14	19 days	M	Laryngeal edema, hyperinflated lungs. Hemorrhage over left temporal lobe. Milk throughout GIT.	1+	Laryngeal edema, tracheal edema. Mild perivascular edema and reactive endothelium in the lung.	Yes
4/10/2018	NC14	7 days	M	Caudal laryngeal edema. Hyperinflated lungs. Milk throughout GIT.	1+	Laryngeal edema, tracheal edema. Perivascular edema in liver and brain.	Yes
4/10/2018	NC 14	13 days	M	Laryngeal/facial, nasal cavity edema. Red arborizing pattern and hyperinflation of lungs. Milk throughout GIT.	3+	Laryngeal and tracheal edema. Minimal perivascular edema. Retinal hemorrhage. Possible neuronal injury in brain.	Yes

Review of procedures

There were no new procedures introduced into any of these round-ups. The processes were all the same and the dye lot being used had been in use for several months. The infants were not anesthetized, did not receive any vaccinations, had a physical exam, eye ointment was applied to help prevent dye from getting in the eyes, had a blood sample collected, received a tattoo, and then received a dye mark. Post-round-up animal technicians observed all animals until fully recovered from sedation, and performed additional checks through the afternoon.

The Nyanzol-D dye mark is used at the Oregon Primate Center, Tulane Primate Center, and at Cayo Santiago in Puerto Rico. The recipe the CNPRC uses calls for warm water, 3% hydrogen peroxide and a measured amount of dye powder. The dye powder is measured out in advance once a new shipment arrives. The measured amounts are placed in Ziploc bags and placed inside an empty container that previously contained the dye powder.

Historically the CNPRC has only applied a small dye mark on the infants back as an indicator that it has undergone a round-up. In recent years, investigators have been using north colony animals as part of their research studies. It is very common for young infants to venture away from their mothers and "play" and investigators requested individual dye marks on the infants in order to determine individual animals when performing observations. This process of dye marking infants at round-up had been going on for several years or more.

After these incidents the dye marks of the dams were listed out and one commonality was that most of the dams have arm dye marks which put the wet dye in close proximity to the dam's nipples.

Conclusions

The initial findings suggested that the infants had exposure to dye that was present on their dam. Although there hadn't been any official change in procedures, the general consensus was that prematurely placing a young infant on an anesthetized dam with a fresh dye mark could increase the opportunity for the infant to get dye on its face, nose and mouth. Subsequent finding supported this conclusion.

Plans Moving Forward

Moving forward the following guidelines to Nyanzol -D dye marking at the CNPRC were agreed upon:

- Infants 6 months and younger will not be dye marked. If there is a special request for dye marking infants < 6 months of age Miss Clairol will be used.
- Infants will be placed on a warming pad when temperatures are cool during round-up, or under the radiant heaters near the staff working the round-up table. All other animals will be placed a distance away from the table for recovery. The plan is that the dams will not look for their infants until they are mostly recovered and the infants who are not anesthetized will not be able to wander into other animals and hopefully minimize the risk of dye transfer onto the infants.
- All animals will have excess dye wiped off after application.

Semi-annual round-ups following the implementation of the steps noted above have since proceeded smoothly without issues involving infants and dye marking. These steps were incorporated into our standard practice.

If you have any questions, please do not hesitate to contact our IACUC Director at (b) (6) or by email at (b) (6), (b) (7)(C) ucdavis.edu.

Sincerely,

(b) (6)

(b) (6), (b) (7)(C)

/pk

c: IACUC
AAALAC

13433-2L



Initial Report of Noncompliance

By: AW

Date: 4/24/18

Time: 12:00

Name of Person reporting: (b) (6), (b) (7)(C)

Telephone #: (b) (6)

Fax #:

Email:

Name of Institution: U of California - Davis

Assurance number: A3433

Did incident involve PHS funded activity? YES

Funding component: _____

Was funding component contacted (if necessary): _____

What happened?

Several rhesus babies died after exposure to a dye

Species involved: Rhesus

Personnel involved:

Dates and times:

Animal deaths:

Projected plan and schedule for correction/prevention (if known): _____

Necropsy, determine cause

Projected submission to OLAW of final report from Institutional Official:

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Case # _____