

**Report on Investigation of Allegations of Noncompliance with the
Public Health Service Policy on Humane Care and Use of Laboratory Animals
at the University of Wisconsin-Madison**

Office of Laboratory Animal Welfare

September 25, 2013

Office of Laboratory Animal Welfare

Report on Investigation of Allegations of Noncompliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals at the University of Wisconsin- Madison

Preface

The Office of Laboratory Animal Welfare (OLAW) herein presents its evaluation, under provisions of the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (Policy), of specific animal related activities conducted at the University of Wisconsin- Madison (UW).

Based on the results of both an internal investigation by UW and a targeted site visit, OLAW determined that although there was no direct noncompliance with the PHS Policy or serious deviation from the provisions of the *Guide for the Care and Use of Laboratory Animals*, the procedures for controlling infection in the cats needed to be enhanced. Standard operating procedures were developed and implemented addressing eye and ear coil maintenance as well as environmental sanitization. Additional revisions were made to the Animal Care and Use Committee approved protocol. These steps were taken in accordance with the PHS Policy which provides institutions a reasonable opportunity to take corrective actions when applicable guidelines involving animal care, treatment or use are not met.

OLAW forwarded this report to UW and People for the Ethical Treatment of Animal (PETA) on September 9, 2013 and invited them to identify any errors of fact in the report.

The UW September 16, 2013 response noted several factual errors and suggested modifications to the text to correct inaccurate statements. OLAW reviewed the suggested changes, made applicable corrections or clarifications to the text, and included the response as Exhibit #35. Specific changes or clarifications are as follows:

- Change abbreviation of UW-Madison to UW rather than UW-M to avoid confusion with the University of Wisconsin- Milwaukee;
- Change "acoustic recording chamber" to "acoustic recording room";
- Change "and to decrease the number of cats used" to "and to conform the description of the number of animals used to actual usage";
- Change "involving nine additional cats on this study" to "nine additional cats in this laboratory";
- Clarify that the "former UW veterinarian who was involved in this study" was "a former UW veterinarian who was infrequently involved in an on-call or substitute capacity as a clinical veterinarian with this study";
- Correct USDA report date to January 16, 2013 (complaint received November 16, 2012; inspection conducted December 10-13, 2012; report issued January 16, 2013); Correct Exhibit #12 title;

- Change outcome of infection with MRSA from “one died” to “one was euthanized after not responding to treatment”;
- Clarify that the February 5, 2013 USDA inspection report noted that a clinical record review identified an accidental burn sustained by a cat sedated for a noninvasive procedure;
- Change heading of “Study Suspension of Invasive Animal Studies” to “Suspension of Invasive Animal Procedures”;
- Change “standard operating procedures (SOP) should be developed” to “standard operating procedures (SOP) should be refined”;
- Clarify the word “generally” from the summary statement “OLAW found that although the specific allegations were generally not substantiated as stated...” to read “...OLAW found that while the allegations did not accurately reflect the entire clinical and research condition of the cats, changes were made to enhance the care of the animals and potentially improve research outcomes...”;
- Change heading in exhibits to correct information on USDA inspection report date and purpose.

The PETA September 16, 2013 response noted a factual error and suggested modifications to the text. OLAW reviewed the suggestions, made corrections as necessary, and included the response as Exhibit #36. The suggestions and actions taken are as follows:

- The source of funding for the study involving Double Trouble was questioned; because the source was clearly determined during OLAW’s investigation not to have been PHS/NIH, no change was made;
- The head cap infection categorization was questioned; this issue has been clearly addressed throughout the report, therefore no change was made;
- The date of the USDA inspection was identified as a factual error and the change was made as also noted by UW; copies of the USDA reports were again included in PETA’s response; these were found to be identical to Exhibit #12;
- The health of the cats currently on study was questioned; the proposed assessment contradicts what had been observed first hand by the site visit team and had also been previously corroborated by the USDA inspector in the January 16, 2013 report, therefore no change was made;
- The willingness of cats to participate in the study was questioned; one cat was specifically observed by the site visit team performing the behavioral tasks and was seen continuing to perform the activity even when no food reward was given (i.e. willingly) and therefore no change was made;

- The use of the word “generally” was questioned by PETA; as noted in response to the same concern raised by UW, this statement has been further clarified (See response above); specific examples of clinical findings and protocol wording were reiterated by PETA but because these had already been addressed in the report, no additional changes were made.

Finding no new evidence that would materially alter the outcome of this investigation, OLAW has not otherwise altered the report.

**Report on Investigation of Allegations of Noncompliance with the Public Health Service Policy on
Humane Care and Use of Laboratory Animals at the University of Wisconsin-Madison**

Background

This report is the result of an investigation of allegations of noncompliance with the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (Policy) against the University of Wisconsin-Madison (UW). A complaint was submitted to the Office of Laboratory Animal Welfare (OLAW) by the People for the Ethical Treatment of Animals (PETA) on September 12, 2012 expressing concerns about the welfare of a cat in a study believed to be funded by the National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health (NIH). The purpose of this study is to obtain information about the neural mechanisms involved in hearing which can help in the design of hearing aids and hearing therapy for humans. The initial submission consisted of 57 pages of daily health records, surgical records, and the approved protocol. The records involved a cat named Double Trouble (L005/G07) and dated from 2006 to 2008 after which the animal was euthanized. An additional 137 pages of material were provided by PETA to OLAW on November 5, 2012 expressing similar allegations involving nine additional cats on the study. Supporting documents consisted of copies of clinical records from 2003 to 2009 which were incorporated with the initial material.

OLAW's authority is derived from the Health Research Extension Act (Public Law 99-158) which is implemented through the PHS Policy, applicable to PHS-conducted or supported research, research training, and biological testing activities involving live vertebrate animals. The Health Research Extension Act provides a reasonable opportunity for institutions to take corrective action when conditions of animal care, treatment, or use do not meet applicable guidelines. Institutions that conduct PHS-supported research are required to have a current OLAW-approved Animal Welfare Assurance (Assurance). The Assurance is a document that verifies that PHS-supported research with live vertebrate animals conducted at the institution is in accordance with the provisions of the PHS Policy. OLAW is authorized to restrict or withdraw approval of an institution's Assurance if that institution fails to correct identified deficiencies.

This Office concluded its evaluation of the allegations and evidence presented by PETA and requested UW, on September 19, 2012, to review and investigate identified concerns regarding the treatment of cat Double Trouble and provide a response. These concerns were categorized according to perceived deviations from the PHS Policy and the *Guide for the Care and Use of Laboratory Animals (Guide)* and involved the specific allegations as well as other aspects of animal care and use identified by OLAW in its review of the evidence. A request for additional information addressing the second set of allegations was sent to UW on January 4, 2013.

Initial Allegation

The allegations from PETA stated that the veterinary care for the cats was inadequate, the Animal Care and Use Committee (ACUC) approved animal activity was not being followed, anesthesia was not properly administered, the numbers of animals used was not properly justified, and that the least invasive procedures were not being used. The records had been obtained from UW under a State of Wisconsin Freedom of Information request and dated back to 2006. PETA requested disciplinary action to be taken against UW and the return to NIH of grant money that supported the study. In addition to the medical records and logs, a US Department of Agriculture (USDA) inspection report was included for an unrelated institution which addressed a different study and species. A procedure log for another cat was also included.

Findings and Evaluation

OLAW investigated the specific allegations as well as related policies and procedures and determined the following:

Funding: The study involving Double Trouble was not funded by NIH.

Veterinary Care: Overall appropriate veterinary care was provided. In addition, since the time the activity addressed in the allegation occurred in 2008, numerous improvements have been made to the animal care and use program, including additional veterinary staffing. Veterinary care and documentation was appropriate. Veterinary care records were updated whenever an important clinical event occurred but no entries were made if there was no problem or veterinarian directed activity. Veterinary care findings included:

- The studies on sound localization performed on cats at UW are being performed to obtain information about the neural mechanisms involved in hearing which can help in the design of hearing aids/cochlear implants and hearing therapy for humans. Because both the eyes and ears are involved in sound localization, delicate electronic devices are used to measure eye movement and nerve impulse conduction. The devices consist of extremely thin wires which are implanted in the eye, brain, and ear during a sterile surgery under full anesthesia. A recording device in a "head cap" is attached to the skull and left in place. This lightweight device looks like a little cap and does not bother the cat but the surrounding tissue and the mechanism must be kept scrupulously clean to prevent bacterial growth. Even with appropriate care, the devices may break and infections occur which require veterinary attention. The cats are maintained on a measured diet and are used in behavioral experiments for which food rewards are given as motivation. An example of this type of experiment consists of the cat responding to a light source in an acoustic chamber (similar to cats chasing lights with laser pointers) and receiving a reward, while readings are being taken through the electronic devices measuring ear and eye movement, and brain response. When not working in the experimental chamber the cats live in cages such as those in a veterinary clinic with hammocks and toys. They receive food and water, use litter boxes, and are provided routine veterinary care. They also have access to an exercise/play room in which they socialize with one another and with people. Because the cats are handled so frequently, they are well adapted to people and appear to willingly perform their tasks, such that they often continue the activity after the recording is completed.

- A non-invasive, nonsurgical two hour auditory brainstem response procedure was performed under anesthesia. In the record, the statement “put in chamber” referred to placing the cat into an acoustic recording room, not placing a head cap. This activity was compliant with the description in the approved protocol.
- During one procedure the cat was intubated and anesthetized; the endotracheal tube became detached from the anesthetic machine during animal repositioning which caused the anesthetic depth to lighten; the tube was reconnected and the deep anesthetic plane was restored; there was no negative impact to the cat and it recovered appropriately; reference to an anesthetic mask was a mistaken entry in the anesthetic log; the research and veterinary staff was retrained on keeping accurate records.
- The analgesic regimen on this study included post-operative administration as well as provision of pain management by veterinarians when clinically warranted. Antibiotic treatment was provided for the intermittent infection around the head cap which was localized and not systemic. The infection site was cleaned, there were no signs of pain due to the infection and therefore analgesic was not needed. However, the condition was not able to be resolved and the cat was ultimately euthanized.

Justification of Animal Numbers: The justification for the number of animals to be used on the study required additional information. The protocol was subsequently amended to address the numbers of animals to be used, to refine the anesthetic regimen, to revise study endpoints, and to conform the description of the number of animals used to actual usage.

Training: All staff members working with research animals are required to complete appropriate training before participating in any animal activities. The Principal Investigator and staff on the cat study were appropriately trained and qualified. The veterinary staff assisted with anesthesia on this study and has subsequently increased its oversight. Refinements in anesthetic technique are ongoing based on evolving practices.

Animal Care and Use Committee (ACUC) oversight: ACUC oversight was in place for the study and continues to be present. All protocols address humane endpoints and veterinary staff is authorized to treat, remove from study, or euthanize animals as needed.

Second allegation: On November 5, 2012 a second complaint was submitted to OLAW from PETA and included similar allegations involving nine additional cats in this laboratory. Supporting documents consisted of copies of clinical records from 2003-2009. Reference was made to corroborating allegations by a former UW veterinarian who was infrequently involved in an on-call or substitute capacity as a clinical veterinarian with this study during that time period. This set of documents was incorporated into the ongoing investigation.

USDA Report: OLAW was in contact with USDA throughout the course of the investigation and was provided with both an October 4, 2012 focused inspection report during which no noncompliant items were identified and the January 16, 2013 inspection report from the visit conducted by the USDA Veterinary Medical Officer (VMO) on December 10-13, 2012 in direct response to the complaints which

had also been made by PETA to that agency. The inspection was directed at the nine cats involved in the second complaint, including a review of relevant records spanning three years. A routine inspection report from February 5, 2013 was also provided. Key findings noted in the inspection reports concluded that:

- there was a pattern of recurring infections involving both the head caps and eye coils utilized in this study;
- eleven cats had been previously diagnosed with chronic infections; one cat required removal of the eye due to infection;
- two cats had been previously diagnosed with Methicillin-resistant *Staphylococcus aureus* (MRSA); although both cats underwent aggressive treatment for the condition, one was euthanized after not responding to treatment;
- none of the nine cats currently present showed signs of infection and were not under treatment for infection;
- the cats undergo positive operant conditioning whereby they are fed in the laboratory in order to foster a positive response; this training consists of “food regulation” that involves monitoring of body weight by both the veterinary and laboratory staff; the VMO found the cats to be in general good health with appropriate body weight;
- the cats were examined and found to be alert, responsive, and interactive;
- in 2008 one cat received antibiotic injections of neomycin sulfate to induce deafness; this resulted in apparent kidney damage which required euthanasia due to deteriorating health;
- in 2012 one cat sustained a burn from a heating pad while under sedation for a noninvasive procedure, the cat was successfully treated, staff was retrained in anesthesia and handling procedures;
- UW was not cited for any noncompliance following a routine February 5, 2013 inspection although a clinical records review noted the accidental burn and acknowledgement was made that corrective procedures have been established to prevent these types of injuries from occurring in the future.

Assessment of Second Allegation:

Regarding the nine cats referenced in the second complaint, OLAW determined that:

- all nine cats were supported by an NIH grant;
- specific refinements made to the study to decrease post-surgical infection associated with head cap implants consisted of performing microbial culture and sensitivity, modifying the care and maintenance procedures for the skin margins around the head cap, and having staff experienced in the care of implants provide additional training to laboratory staff;

- none of the cats dropped below an established weight-loss threshold; the veterinary staff are involved in determining if the cats are in discomfort and if euthanasia is necessary;
- the cats are deeply anesthetized for all surgical procedures; for any potentially painful procedures analgesics are given preemptively and post-procedurally;
- refinements in anesthesia techniques have been ongoing and include use of a wider variety of analgesics and additional dosing routes; refinements in application of the eye coils is ongoing to enhance success of the device and reduce breakage; the application route of neomycin to induce deafness has been changed to prevent unintended kidney damage.

Suspension of Invasive Animal Procedures: OLAW consulted frequently with key individuals at NIDCD during the course of the investigation and a decision was made in April 2013 to suspend all invasive activities involving live vertebrate animals in this study in the interest of animal welfare, to protect research quality, and to prevent the introduction of additional variables. A letter was issued by the NIDCD Chief Grants Management Officer on April 10, 2013 to the UW Director of Research and Sponsored Programs directing the suspension of all invasive animal activities. These activities included electrophysiological recordings, implantation or placement of instrumentation into or onto animals, collection of biological samples from animals, and the sedation of animals. During the suspension, no charges associated with invasive animal activities were allowed to be made to the grant. Manipulation of the cats was allowed to maintain instrumentation, to continue behavioral training, and to provide general health and welfare support.

OLAW Site Visit and Recommendations:

In order to directly assess the condition of the cats and their environment, the Director of the OLAW Division of Compliance Oversight conducted a site visit on April 17-18, 2013 to UW accompanied by an NIH veterinarian who is a subject matter expert in the care of animals with head cap implants and by a senior veterinarian from the USDA Eastern Sector Animal Care office. The team conducted physical exams on the seven cats currently remaining on the study; examined the housing area, laboratory, and acoustic recording room; reviewed the techniques used to maintain the head caps on the cats; reviewed relevant records; observed the cats being handled, transported, and performing a behavioral task; and discussed the care of the animals with the Principal Investigator (PI), Attending Veterinarian (AV), clinical veterinarians, technicians, animal care staff, ACUC members, Institutional Official, and other senior leaders involved in the animal care program. The team's findings are as follows:

- all seven cats were found to be in excellent clinical condition, namely having good body condition, good hair coats, were very well socialized with the other cats as well as people, and exhibited normal behavior;
- one cat was observed performing in one of the approved behavioral study procedures and was found to be a willing participant;

- none of the cats showed any lesions or signs of pain, distress, or adverse responses during handling, transport, examination, or during the experimental trial;
- cats were demonstrated entering cat carriers or restraint bags cooperatively on command when shown the objects;
- the AV and clinical veterinarians were knowledgeable and caring and were familiar with the cats, their clinical conditions and history, as well as the details of the study;
- the animal care supervisor and caretaker were familiar with the sanitization procedures for the cats' primary housing, their hammocks, and related equipment and readily provided documentation of appropriate cleaning regimens;
- the PI and technicians were very concerned about the wellbeing of the cats and handled them carefully and gently during transport and behavioral trials; they monitored the animals closely while the cats were performing tasks in the specialized acoustic recording room;
- all individuals involved with handling and observing the cats were trained in the recognition of signs of pain or distress, and verified that any animal health concerns are promptly reported to the veterinary staff; veterinarians are empowered to remove animals from study if wellbeing is in question;
- refinements made to the study since its inception included enhanced veterinary oversight and support during surgeries, stricter oversight of fluid and anesthetic administration during surgery, and improved overall monitoring;
- review of the medical records showed that superficial infections of the skin tissue surrounding the head caps have occurred sporadically over the past six years in these cats and were treated successfully.

Recommendations were made by the site visit team to further enhance the health and welfare of the cats and are as follows:

- provision of environmental enrichment for the cats should continue but should occur in a designated play area that can be readily sanitized including the floors, walls, and any climbing and resting structures; frequent interaction with people and the other cats should continue;
- laboratory specific standard operating procedures (SOP) should be refined addressing cleaning, sanitization, and sterilization of all equipment used for head cap care; these performance standards are to be developed in consultation with the veterinary staff, applied to all surgical tools, sterilizing chemicals, feeding tubes, head hardware, restraints, probes, and other devices, and reviewed and approved by the ACUC;
- environmental contaminants must be controlled and pathogen transmission between animals eliminated; adequate infection control must be exercised; should infections recur the veterinary staff is to perform a root cause analysis and take appropriate preventive action;

- the PI and veterinary staff are to remain current with ongoing advances in the care and maintenance of head caps and related hardware and are to communicate with other experts in the field to remain informed of current best practices;
- ACUC review of the rewritten protocol should evaluate the use of the cat as the only acceptable model for this study and examine the number of animals requested; the protocol is to clearly outline each procedure, provide specific humane endpoints, and contain no ambiguous information; the ACUC is to balance the potential adverse effects on an individual animal against the potential scientific value to be obtained and make this a primary consideration in the review process; the PI should keep NIH officials informed of any unexpected or unusual events which occur during the course of the study.

Resolution: On August 21, 2013 UW confirmed resolution of OLAW's concerns. 1) Copies of the laboratory SOPs addressing maintenance of the head caps, eye coils, and ear coils; animal transportation; food preparation and equipment maintenance; non-surgical procedures with or without anesthesia required; and animal equipment cleaning were provided. 2) A cat socialization and behavioral training room was established and SOP developed regarding its maintenance. 3) An infectious disease specialist at the School of Veterinary Medicine assisted in developing best practices to reduce or eliminate the potential pathogen transmission between animals and will be available for consultation to the ACUC as needed. 4) The rewritten protocol was reviewed by the ACUC and approved on August 26, 2013 and copy was provided to OLAW.

OLAW received and accepted these documents and concurred with the actions taken by the ACUC and closed the active portion of the investigation on August 29, 2013. OLAW will continue to monitor this study to ensure that all procedures are conducted in accordance with the PHS Policy and other relevant laws and guidance documents.

Summary: OLAW found that while the specific allegations did not accurately reflect the entire clinical and research condition of the cats, changes were made to enhance the care of the animals and potentially improve research outcomes. Specifically, there was a need to enhance infection control in the environment and the cleaning procedures for the tissue surrounding the head cap, maintenance of the implant, and care of the surgical equipment. To further prevent environmental contamination, the cats were provided with a dedicated play area that can be sanitized. The protocol was amended to more clearly justify the numbers of cats required and the ACUC conducted a harm-benefit analysis weighing the procedures conducted with the cats against the potential benefits of the information to be obtained.

In the interest of animal welfare and the protection of research quality, the invasive animal activities were suspended by NIDCD during OLAW's investigation for approximately six months. Upon successful implementation of OLAW's recommendations the matter was closed. It is anticipated that the suspension will be lifted to allow the full scope of the study to resume under enhanced oversight. OLAW will continue to monitor the status of this activity.

The University of Wisconsin- Madison

Exhibits

- 1) Letter dated September 12, 2012 from PETA, presenting the allegation and requesting disciplinary action against the University. The supporting documents included clinical records, an unrelated USDA report, and a 2008 version of the protocol. This letter was also sent to the NIH and NIDCD Directors.
- 2) September 12, 2012 acknowledgement from OLAW to PETA that the complaint was received.
- 3) September 12, 2012 email from OLAW to NIDCD Director indicating that OLAW will assess the complaint and investigate the matter if warranted. A point of contact was identified at NIDCD.
- 4) September 19, 2012 letter from OLAW to Institutional Official (IO) at UW posing specific questions regarding clinical veterinary record keeping, training of research staff, provision of analgesia, and humane endpoints.
- 5) October 11, 2012 interim report from UW IO indicating that the Animal Care and Use Committee (ACUC) was addressing the questions.
- 6) October 16, 2012 email from USDA Assistant Eastern Regional Director setting up a conference call. Also attached was a copy of an October 12, 2012 letter to the USDA Inspector General from a former UW veterinarian who presented an opinion on the treatment of the cats.
- 7) November 5, 2012 letter from PETA regarding 9 additional cats on the study. Copies of the clinical records were provided for these animals.
- 8) November 7, 2012 acknowledgement from OLAW to PETA that the information was received.
- 9) December 27, 2012 letter from UW IO responding to OLAW's questions.
- 10) January 4, 2013 letter from OLAW to UW discussing the responses and posing additional questions. More information was requested regarding the second set of allegations.
- 11) January 31, 2013 letter from UW IO providing an interim report.
- 12) Copy of January 16, 2013 and February 5, 2013 USDA inspection reports. The earlier inspection was specifically made to address the PETA complaint about the cats and the latter was routine. Pictures of some cats were included.
- 13) March 11, 2013 reply from UW IO addressing OLAW's questions.

- 14) April 11, 2013 letter from OLAW to UW IO indicating that a site visit would be conducted on April 17 and 18 by OLAW. The site visitors included the OLAW Director of the Division of Compliance Oversight, an NIH subject matter expert veterinarian, and a senior USDA veterinarian.
- 15) May 7, 2013 letter from OLAW to UW IO outlining the findings of the site visit and listing specific recommendations.
- 16) July 8, 2013 letter from UW IO providing an interim report on the status of the recommendations.
- 17) August 21, 2013 letter from UW IO providing information on the implementation of the recommendations.
 - a) Eye & ear coil maintenance standard operating procedure (SOP)
 - b) Non-surgical procedures: No anesthesia SOP
 - c) Sanitization of cat socialization and behavioral training room SOP
 - d) Animal transportation SOP
 - e) Animal equipment cleaning SOP
 - f) Explant maintenance SOP
 - g) Non-surgical procedures: Anesthesia required SOP
 - h) Copy of amended protocol dated 8/26/13 submitted subsequently
- 18) August 29, 2013 letter from OLAW acknowledging the implementation of the recommendations and indicating that the case would remain open although no additional information was currently needed.

Additional Supporting Documents

- 19) April 10, 2013 letter from NIDCD Chief Grants Management Officer (GMO) to UW Director of Research and Sponsored Programs suspending invasive animal activities.
- 20) April 11, 2013 acknowledgement letter from UW Research and Sponsored Programs.
- 21) April 16, 2013 email from Chief, NIDCD Office of Health Communication and Public Liaison regarding number of call and emails received regarding the cats.
- 22) March 18, 2013 letter from PETA submitting November 16, 2012 USDA inspection report; March 20 OLAW acknowledgement of receipt.
- 23) March 22, 2013 response to select public inquiries regarding UW research.
- 24) May 3, 2013 letter from NIDCD Chief GMO providing a status update on suspension.
- 25) September 2012 PETA rebuttal to UW statements.

- 26) September 8, 2008 ACUC minutes covering discussion of cat protocol.
- 27) October 4, 2012 USDA focused inspection report of UW; no noncompliant items found.
- 28) October 10, 2012 NIH eSNAP report of protocol.
- 29) Site visitor thank you letters and conflict of interest and confidentiality certification.
- 30) January 23, 2013 email from Office of Management Assessment regarding Office of Inspector General (OIG) Hotline Complaint.
- 31) February 7, 2013 OIG Hotline complaint.
- 32) Three media articles regarding the case.

Request and Response Regarding Identification of Errors of Fact

- 33) September 9, 2013 letter to UW requesting identification of errors of fact
- 34) September 9, 2013 letter to PETA requesting identification of errors of fact
- 35) September 16, 2013 response from UW IO identifying and correcting errors of fact
- 36) September 16, 2013 response from PETA identifying and correcting errors of fact