

External Review

Adverse Event*

Death of an Adult Rhesus Macaque on May 12, 2023

**External Reviewer: Christian R. Abee, D.V.M., M.S., DACLAM
Professor Emeritus, University of Texas
MD Anderson Cancer Center**

Date: August 21, 2023

***Adverse Event: Unexpected incident that leads to harm, or endangers the well-being of animals and humans at a research facility. *Lab Animal* 2017; 46(6):244-249**

Incident Under Review:

An adult female Rhesus Macaque was euthanized for humane reasons following transport to an offsite [REDACTED] facility on May 12, 2023.

Purpose of the Review:

The [REDACTED], [REDACTED], requested an external review of this incident to include a written report with conclusions and recommendations. The review was charged with determining the factors that contributed to the May 12, 2023 death of the adult female rhesus macaque and to provide recommendations on remedial measures to ensure there can be no repeat of this incident.

External Reviewer:

Christian R. Abee, D.V.M., M.S., DACLAM
Professor Emeritus, Department of Comparative Medicine
Former Director, Michale E. Keeling Center for Comparative Medicine and Research
University of Texas MD Anderson Cancer Center

Review Process:

The external review included televideo interviews by Zoom, a review of documents related to the incident provided by the program, and a one-day site visit to understand the procedures and processes used on the day of the incident, observe equipment used on the day of the incident, and meet with the staff involved in the incident.

The following staff of UC Davis and the CNPRC were interviewed by Zoom between July 12 and July 27, 2023:

[REDACTED], [REDACTED], UC Davis Research and Teaching Animal Care Program

[REDACTED], CNPRC
[REDACTED], CNPRC
[REDACTED], CNPRC
[REDACTED], Laboratory
[REDACTED], Laboratory
[REDACTED], CNPRC
[REDACTED], CNPRC
[REDACTED], CNPRC
[REDACTED], CNPRC
[REDACTED], CNPRC
[REDACTED], CNPRC

The following faculty and staff were interviewed during the site visit on July 21, 2023:

[REDACTED], UC Davis Animal Care Program
[REDACTED], CNPRC
[REDACTED], CNPRC
[REDACTED], CNPRC
[REDACTED], CNPRC
[REDACTED], UC Davis
[REDACTED], CNPRC

Documents Reviewed:

1. [REDACTED]
2. [REDACTED]
3. [REDACTED]
4. [REDACTED]
5. [REDACTED]
6. [REDACTED]
7. [REDACTED]
8. [REDACTED]
9. [REDACTED]
10. [REDACTED]
11. [REDACTED]
12. [REDACTED]
13. [REDACTED]
14. [REDACTED]
15. [REDACTED]

Adverse Event of May 12, 2023 and Incident of July 17, 2023

May 12, 2023

On May 12, 2023, two adult rhesus macaques were transported from the CNPRC to the [REDACTED] facility. The animals were transported in a cargo van used by the CNPRC that was equipped to transport nonhuman primates in stainless steel cages. These animals were boxed and moved to the van between 8:00-8:15 am. The drive to the [REDACTED] facility took approximately 15 minutes and the animals arrived at [REDACTED] at approximately 8:30 am. The [REDACTED] procedure required the animals to be [REDACTED] one at a time. The first animal was sedated and moved to the preparation area of the [REDACTED] facility while the second animal remained in the van until the first [REDACTED] procedure could be completed. The temperature on the morning of the incident was in the low 60's rising to 74 degrees by 11:00 am. Between 8:00 and 8:15, the staff members transporting these animals turned on an aftermarket, forced air heating unit that was mounted above the transport cages in the van. This heating unit had a single setting for heat that blew a strong heated stream of air from the heater vent through the wire mesh ceiling of the transport cages that were located directly below the vent. According to the document provided by UC Davis Fleet Services dated June 26, 2023, the vent temperature from this forced-air heater was measured at 130 degrees F. Because this heating unit did not have a thermostatic control, continuously heated air was blown from the vent. On the day of the adverse event, the heater vents were adjusted to blow directly into the cages that were positioned below the heater vents.

At about 8:30 am, the first animal was sedated and moved into the preparation area of the [REDACTED] facility. Various accounts of staff estimated that the remaining animal was last observed and appeared not to be in distress between 8:45 and 9:00 am. The first animal had an elevated heart rate that required attention of the technicians and delayed the [REDACTED] procedure. The second animal in the transport van remained unobserved for 50 to 90 minutes (accounts of staff vary) while the heater continued to blow forced, heated air into the cage housing this animal. When the SRA returned to the van to sedate the second animal, the animal was found comatose, lying in lateral recumbency on the floor of the cage. The animal was immediately removed from the cage and carried into the preparation area of the [REDACTED] facility where resuscitation procedures were begun. These included intravenous fluid administration, wiping down the animal's head and body with towels soaked in cool water. A veterinarian was contacted. The veterinarian and an Animal Health Technician Supervisor arrived at [REDACTED] approximately 30 minutes after the comatose animal was discovered. During the wait for the veterinarian, resuscitation procedures and cooling efforts were continued. When the veterinarian arrived, the animal's body temperature was recorded at 104.7 degrees. This body temperature measurement was obtained approximately 30-40 minutes after cooling procedures had begun. Staff members who discovered and attempted resuscitation commented that the metal surfaces of the cage housing this animal remained very warm for an extended period after removing the comatose animal.

The animal was transported back to the CNPRC at approximately 11:30 am and Intensive Care Procedures (ICU) were initiated. The animal's pupils were noted to be fixed and dilated. Fluid administration was continued. The animal began experiencing seizures at about 12:30. Valium (diazepam) was administered. The animal remained comatose. Shortly thereafter, the veterinarians made the decision to perform euthanasia. Euthanasia was carried out followed by immediate postmortem examination (necropsy).

A complete necropsy was done including both gross and microscopic examination. The extensive nature of the lesions observed in all organ systems supported the decision of the clinical veterinarians to euthanize the animal. Although some age-related conditions were observed grossly and microscopically that could have impaired the animal's ability to respond to heat stress, the severity of the observed acute injury to multiple organ systems and known environmental factors establish the cause of death as acute severe hyperthermia leading to euthanasia.

July 17, 2023

A second incident that occurred on July 17, 2023 is included in this report because it provides additional insight into the adverse event under review. After May 12, transport procedures were modified so that only one animal at a time would be transported for [REDACTED]. This eliminated the need for an animal to wait inside the van. On July 17, the transport van had a recorded temperature of 98 degrees prior to transport. The animal technicians stated that it did not feel uncomfortably hot inside the cargo area. They attributed the high temperature reading to the location of the temperature monitor which was hanging close to the panel wall of the van which was a warmer area than the cage area. The air conditioning unit was turned on to cool the inside of the cargo area of the van. The animal was loaded and transported to [REDACTED] for [REDACTED]. The animal was sedated and moved into the airconditioned preparation area immediately upon arrival. Preparing the animal for [REDACTED] required 10-15 minutes. The SRA who prepared the animal noticed that the animal felt hot. The rectal temperature was 104.2 F. Out of concern that the van may be too hot to transport an animal, the SRA went to the van to ask about the temperature of the van's cargo area. The animal technicians in the van stated

that the temperature monitor showed 89 F. This was at least 30-40 minutes after the air conditioner was turned on prior to transport from CNPRC. The animal care technicians were both aware of the animal death on May 12, but did not consider the temperature inside the van to be a serious concern. The SRA requested that they refrain from transporting back to CNPRC until the temperature of the cargo area dropped to 80 F. The animal technicians did not appear to take this request seriously assuring the SRA that the temperature was fine. Regardless, they waited until the temperature had reached 78 F before transporting.

Although the animal transported on July 17 did not show clinical signs of heat stress, it is important to note that a temperature of 104.2 is significantly elevated. Furthermore, this animal's temperature may have been above 104.2 upon arrival at [REDACTED] because the temperature measurement was not taken until after the animal had been in the airconditioned preparation area for at least 15 minutes. This animal was exposed to an elevated temperature during transport for a much shorter period than the animal that died on May 12, but still had a high body temperature. This incident (July 17) suggests that the elevated heart rate of the first animal [REDACTED] on May 12 may have also been the result of heat stress because a common early clinical sign of heat stress is elevated heart rate. This incident demonstrates that hyperthermia can occur rapidly during the transport process. It is noteworthy that the technicians transporting the animal did not notice that the animal was experiencing an elevated body temperature nor were they concerned that the temperature of the cargo area of the van might be dangerous for the animal.

Site Visit Description and Findings:

The site visit was carried out on July 21, 2023. The purpose of the site visit was to allow the external reviewer to gain direct experience with the transport van, the heater, and other equipment used for transport of animals from the CNPRC to the [REDACTED] facility. The site visit also provided the opportunity to simulate some of the conditions of May 12, 2023 to gain direct experience with temperatures inside the van.

The site visit included meeting with the [REDACTED] SRAs who transported the animal on May 12, 2023. They provided a detailed account of the events that day. Following this meeting, Dr. Abee and the SRAs met inside the animal transport compartment of the cargo van. The van was equipped with identical cages as those used when the adverse event occurred. Dr. Abee asked the SRAs to turn on the heater just as it was on the day of the event and requested measurements of temperatures for 30 minutes while the SRAs and Dr. Abee remained in the cargo area. Temperatures were measured at the level of the cage that housed the animal. At approximately 25 minutes into the test of the heater operation, the temperature at cage level exceeded 110 degrees F. All metal surfaces of the cage were uncomfortably hot to touch. The cage used for transport had solid metal side and back panels with wire mesh on the floor, cage front, and cage ceiling. The heated metal surfaces radiated heat into the cage in addition to the convection heat from the forced air heating vent. It is also important to note that the animal housed in the cage on May 12 was in direct contact with these heated metal surfaces. Within the period of the test run of the heater, the cargo area became uncomfortably warm far exceeding the 85-degree transport temperature specified in the Animal Welfare Act.

The site visit also included an interview of the SRA who noticed the elevated temperature of the animal during the July 17 incident. This interview included a description of [REDACTED] interaction with the animal care technicians responsible for transporting the animal that day.

Conclusions:

1. The adverse event of May 12, 2023 that led to euthanasia for humane reasons of an adult female rhesus macaque was caused by extensive, multisystem injuries resulting from acute hyperthermia (heat stroke).
2. The source of heat leading to hyperthermia was a heating unit mounted above the cages in the van used to transport animals from CNPRC to the [REDACTED] facility.
3. Due to technical problems with the first animal that was [REDACTED] on May 12, the second animal was left unattended and exposed to high temperatures for an extended period.
4. The heating unit's lack of thermostatic control resulted in an increase in temperature within the transport cage beyond physiologically tolerable levels.
5. The factors leading to this adverse event were not anticipated within the SOP nor from prior experience transporting animals to the [REDACTED] facility.
6. This incident could have been prevented if the heater in the transport van had been thermostatically controlled, and/or if the animal had not been left unattended for an extended period while the first animal was being [REDACTED].
7. The second incident on July 17 involving another rhesus macaque provides useful insight into the May 12 adverse event by showing that even short periods of exposure (15-20 minutes) to elevated temperatures during transport can result in hyperthermia.

Recommendations:

1. The SOP for transport of animals to offsite facilities should be rewritten considering what was learned from the May 12 and July 17 incidents.
2. SOPs should consider the age and clinical conditions of animals undergoing procedures and modified as necessary to reduce hazards to animals that may have impairments due to age or other clinical condition.
3. All animal areas whether for transport, holding, short term housing, or long-term housing should be heated and cooled using thermostatically controlled heating and cooling systems.
4. The SOP for transporting animals should be modified so that there is adequate staff support to maintain frequent observation of animals (at least every 10 minutes).
5. When animals are transported outside the CNPRC, they should not be left unattended in the transport vehicle.
6. Temperatures during animal transport should be strictly maintained within the temperature range specified in the Animal Welfare Act. If this is not possible, the animal should not be transported.
7. Technical staff responsible for carrying out procedures with animals should be trained to be sensitive and responsive to the concerns of fellow staff members in matters of animal welfare.
8. The CNPRC should consider this adverse event as rationale for carrying out a review of all SOPs currently in use with an emphasis on making certain that animal welfare and safety are primary considerations. In addition to assuring the safety of animals, this action will further demonstrate to scientific and technical staff and regulatory authorities the importance the center places on animal welfare and wellbeing.