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Delay between adaptation and experimentation

Gradual adaptation of her rats to a restraint device seemed a logical and obvious strategy to Dr. Julia Marshall, a neurophysiologist at Great Eastern University. Her research focused on ocular responses to external stimuli, and her methodology required that the head of each rat that she used be immobile, although the remainder of the torso did not require full restraint. Her IACUC-approved adaptation protocol had three steps: first, a rat was placed into an empty plastic restraint tube once a day for three days; second, the rat was anesthetized and allowed to awaken in the tube once a day for three days; finally, the rat was lightly anesthetized, its head placed in a special restrainer within the plastic tube, and again allowed to awaken in the restrained

position once a day for three days. The rat would remain in the tube for 30 minutes during the first session, then 45 minutes for the second session and finally for 60 minutes at the last session. After the conditioning was completed, the study, which lasted five consecutive days, would begin. A total of 15 rats would be tested, all requiring head restraint.

Marshall had used the same basic protocol for many years without a problem. The occasional rat that did not adapt to the restraint device was excluded from her study. But just before the most recent testing session, Marshall's long-time research associate took ill, and the testing had to be delayed for a little over a week. The delay was quite obvious to the vivarium staff because the testing room was ready but

unused. The attending veterinarian asked Marshall about her plans to 'readapt' the animals before the testing started, but Marshall said that wasn't necessary because the rats had already been adapted to the restraint procedure. The veterinarian could not find any literature about the length of time a rat could remain adapted to a restraint procedure after a break in a testing protocol. When Marshall also could not produce any documentation relative to her model, the issue was quickly given to the IACUC. Unfortunately, the IACUC could not locate an expert who could confirm or refute Marshall's opinion, and so the issue seemed to be headed for a stalemate.

What steps do you think the IACUC could or should take to resolve this problem?

RESPONSE

Pilot study

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The IACUC is faced with a difficult decision. If the Committee allows the study to continue without 'readaptation' to the restraint device, there is the potential for the rats to experience unnecessary or increased distress. If the IACUC requires 'readaptation' of the rats, the study will be further delayed. At the onset, there is a deviation in the experimental design with regard to the time interval from the initial training event to the start of the study. Depending on the verbiage in the approved protocol, continuing the experiments could be considered non-compliance. If the IACUC determines that the currently approved protocol does not allow for an alteration in the interval

between adaptation and initiating the experiment, and that this change constitutes a "significant change" (Public Health Service *Policy on Humane Care and Use of Laboratory Animals* (PHS Policy), section IV.C.1)¹ owing to the potential for increased distress, then the IACUC should require Marshall to submit an addendum to her protocol. Another factor the IACUC needs to address is the protocol approval process timeline.

There is also the potential that the data collected from this group of rats won't be valid due to the time variable introduced. Requiring 'readaptation' of the rats would also introduce another variable into the study. Depending on the length of time it takes for the addendum to be approved, the rats that have already been adapted may not be good research models. The IACUC also needs to take into consideration what will happen to this group of animals if Marshall determines that they cannot be used for these experiments.

In order to ensure compliance with the PHS Policy, the IACUC should require that an addendum be submitted to cover the change in schedule. If there is truly no literature to support Marshall's argument that the rats do not need to be 'readapted,' then she could propose a pilot study with this group of rats to determine whether the delay in the beginning of data collection affects the outcome of the experiments or results in increased distress to the rats. The IACUC could approve starting with five of the fifteen rats and grant approval for continuing with the remaining rats if Marshall presents evidence that the rats have remained adapted to the restraint. Marshall will need to include criteria that can be used to determine that the rats do not show increased stress compared with those used in her previous experiments. Such a pilot study would allow the protocol to be further modified with flexibility in the time interval between adaptation and data collection so that delays in the future will not result in non-compliance.