

ATTACHMENT to APHIS FORM 7023 (93-R-0440), Federal Fiscal Year 2011/2012

- 3. The following are the locations where regulated animals were housed or used during the year [Section 2.36(b)(4)]:



Column E:

The University of California at San Francisco is committed to using laboratory animals in such a way as to minimize pain or discomfort. The Committee reviews each project and many protocols have been redesigned to meet this goal. Attached are the explanations of the procedures producing pain or distress in the animals covered by Subchapter A - Animal Welfare and reported in column E during the period 10/1/11 through 9/30/12 and the reasons anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretations of the research. Separate Optional Column E form (1) is attached.

COLUMN E EXPLANATION

- 1. **Registration Number:** 93-R-0440
- 2. **Number of animals used in this study:** 195
- 3. **Species (common name) of animals used in the study:**
New Zealand White Rabbit
- 4. **Explain the procedure producing pain and/or distress.**

Staphylococcus aureus, particularly community-associated methicillin-resistant Staphylococcus aureus, causes severe infections and high mortality rates, particularly in patients with pneumonia. Rabbit models reproduce many of the important features of staphylococcal pneumonia as they occur in humans. Rabbits also exhibit pathogen-host specificities that are similar to humans. Our goal is to use the rabbit pneumonia model to further define bacterial factors that are important in virulence and pathogenesis of pneumonia caused by *Staphylococcus aureus* and to test various therapeutic approaches (antibodies-based therapies, vaccination, antimicrobials) for treatment of these severe infections. To establish bacterial infection, *S. aureus* inoculum is instilled endobronchially through a soft catheter positioned via an endotracheal tube in an anesthetized animal.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For federally mandated testing, see Item 6 below).

These infection models produce few, if any, early indicators of distress or discomfort that can be used to guide interventions to relieve either condition. These are also particularly severe infections, both in rabbits and in humans, the latter suffering a 25-40% mortality rate even when appropriate therapy is administered. The rapidity with which the infection can advance in some animals also defies prediction of distress or discomfort. Other than administration of fluids,

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interventions short of euthanasia (e.g., administration of antibiotics or analgesia) would invalidate the model by altering the natural progression of the disease which is under study, alter the pathophysiology or host response, or hasten death. Deaths are possible in these infection models and they cannot be accurately or reliably predicted in the individual animal. Monitoring parameters such as fever do not accurately predict outcome. Approximately 20% of animals with bacteremia, for example, survive with no apparent ill effects other than fever and modest weight loss. About half of the rabbits manifest sufficient weight loss, are moribund or otherwise unable to access food and water. These appear to correlate with extent of disease and can be useful endpoints in competition experiments in particular. Animals with these findings are removed from the study. Yet, up to half or more of rabbits die and they do so without manifesting findings of severe disease. There are no early indicators short of death or moribund condition that can be used as a clinical endpoint that would allow us to define the outcome of interest: whether the host clears the organism or not from the target tissue or tissues under study. Due to the inability to predict death in individual animals, all animals are potentially at risk for unrelieved distress and death. Accordingly, all infected animals will be classified as category E.

6. What, if any, Federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

NA

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UCSF IACUC-APPROVED REPORTABLE EXCEPTIONS

Exceptions from the Exercise/Psychological Well-being Plan

Species: Monkey, Cynomolgus or Rhesus Macaque

Number of Animals Used: 13

DESCRIPTION: 13 Cynomolgus macaques were given MPTP neurotoxin to create a model of Parkinson's disease. These animals were then involved in a 1-12 month treatment efficacy study and were individually housed for the duration of the study. Animals enrolled in these studies involved clinical behavioral assessments and response to drug therapies (mainly L-dopa, amphetamine, and apomorphine) and required single housing conditions during the study for behavioral data collection. Pair housing would potentially invalidate the data collected. Housing conditions must be kept constant in both the pre- (baseline) and post-treatment (gene therapy) conditions in order to validate results of the study. Any change/improvement in behavioral signs cannot be attributed exclusively to the therapy, but may in fact result in part from increased stimulation.

Maintaining Animals at Temp/Humidity Outside Standards, Not Providing Diurnal Lighting as Required

Species: Hamster

Number of Animals Used: 0

DESCRIPTION: At approximately 3-6 months of age, 40 animals will undergo the hibernation experiment.

Female Turkish hamsters between 3-6 months of age will be housed individually in rat cages and placed in short day cycle (8 hours light/16 hours dark for 2 weeks).

10 of them (per experiment) will not undergo hibernation, and will be housed at controlled room temperatures for the next 8 weeks.

30 out of the 40 animals (per experiment) will be placed in the cold room (4 degrees Celsius), also on a short day cycle, to induce hibernation. The animals will have food and water available to them at all times for consumption during their intermittent periods of arousal. The animals will hibernate for 8 weeks duration. The animals and their hibernation status will be checked every 24h by placing a small piece of paper on the back of the hibernating animals. The presence of the paper will confirm hibernation over the preceding 24h period.

After 8 weeks, 10 animals in hibernation will be euthanized by decapitation alone (this is due to very low respiratory and low circulatory rates which preclude the use of a chemical anesthetic.) and their heads collected for analysis of the teeth.

Another 10 hibernating animals will be taken out of the cold room and kept at room temperature, which will induce arousal after 1h. The aroused animals will then be euthanized by CO2 administration and decapitation or bilateral thoracotomy and heads will be collected for tooth analysis.

Another 10 animals will be taken out of the cold room and left at room temperature for 2 weeks, after which these 10 animals (post-hibernation) will be euthanized by CO2 administration and decapitation or bilateral thoracotomy and heads will be collected for tooth analysis.

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The 10 non-hibernating animals will be euthanized by CO2 administration and decapitation or bilateral thoracotomy and heads collected for tooth analysis.

The animals are checked daily and provided fresh food and water. The cages are changed every 2 weeks during hibernation. This frequency is justified due to the low metabolic rate of the animals. The Relative Humidity (RH) in the space will be kept between 30 – 70%.

Reportable Exceptions - Not Cleaning/Sanitizing at Required Frequencies

Species: Vole

Number of Animals Used: 9

DESCRIPTION: Exposure to dirty bedding for sentinel surveillance:

Cage changes occur once or twice a week depending upon how soiled they are. At cage change, a small amount of dirty bedding is placed in the sentinel animals' clean cage as a means of monitoring the health status of the colony of animals. There are two sentinel cages for every two racks. One cage houses a sentinel mouse and the other sentinel cage houses two sentinel voles. A small amount of dirty bedding is transferred weekly to each sentinel cage from each of the animals' cages located on that rack.

The sentinel mouse is screened quarterly using our standard serology panel and the voles are screened quarterly for ectoparasites and endoparasites. After cages are changed, all dirty cages are cleaned and sanitized in our cage wash facility.

Reportable Exceptions – Fluid Regulation – Section 3.83

Species: Monkey, Cynomolgus or Rhesus Macaque

Number of Animals Used: 10

DESCRIPTION: Fluids or food is regulated in our animals to motivate them to perform the behavioral task that allows us to investigate questions of how brain circuits generate behavior.

Note that individual animals will never be both food and fluid regulated at the same time.

Please note that even these reported animals rarely, if ever, experience a situation where they are not provided potable water twice per day per AWA regulations. We voluntarily report this exception to be conservative in our reporting.

Species and Numbers

Reportable Exceptions – Innovative Housing – Sections 3.84

Cynomolgus and Rhesus Macaque Monkeys

Number of Animals Used: 19

DESCRIPTION: In order to provide certain nonhuman primates with enhanced physical environments, members of these species are occasionally placed into large “play cages” or “activity modules”. Typically nonhuman primates are rotated through such cages. The number

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of such animals varies, but is approximately **19** NPH during this reporting period. The hard surfaces of the play cages or activity modules are spot cleaned and all excreta or disease hazards removed between individuals. These enclosures are sanitized on a normal schedule. Because many of the NHP are paired housed, they constitute a single group of animals for health status. The rotations are often enough that full sanitation between individuals would require frequent dismantling of exercise cages and pens for sanitization and decrease the amount of time it is available for animal use. Individual animals would receive much less opportunity for experiencing this enhanced caging. Clearly the result would decrease this institution's efforts and ability to invoke a creative and positive animal housing experience.

This reportable exception to Section 3.84 of the AWAR - innovative housing - was reviewed and approved by the IACUC at the April 19, 2005 convened meeting of the full committee. Therefore, this institution reports that as it relates to sanitation between individuals.

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