OMB APPROVED
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Interagency Report Control No. 0180-DOA-AN

Fiscal year:

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

Annual Report of Research Facility
Column E Explanation

(TYPE OR PRINT)

This information is required by law (7 U.S.C. 2143 and 9 C.F.R. §2.36). Failure to report according to the regulations can result in an order to cease and desist.

1. REGISTRATION NUMBER	**2. Research Facility Headquarters address**
3. Number of animals used in the study.	**4. Species (common name) of animals used in the study.**

5. Explain the procedure producing pain and distress.

6. Provide the scientific justification for not providing the appropriate anesthetics, analgesics, or tranquilizing drugs during procedures where the animal experienced accompanying pain or distress greater than momentary or slight.

7. 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):

Agency	**CFR**

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51- R- 0018

2. Research Facility Headquarters address

University of Maryland Baltimore
10S Pine Street
MSTF Building, Room G100
Baltimore, MD 21201

3. Number of animals used in the study.

50

4. Species (common name) of animals used in the study.

Guinea Pig

5. Explain the procedure producing pain and distress.

Animals will be exposed to a supra-lethal dose of the pesticide chlorpyrifos, which could induce severe signs of acute toxicity, including profuse secretions, convulsions, and respiratory distress. These animals will receive therapeutic intervention (conventional antidotal therapy), however depending on the dose of the antidotes, it is anticipated that 20-30% of animals may still experience acute signs of toxicity. Animals will be euthanized as soon as signs of acute toxicity become life-threatening.

6. Provide the scientific justification for not providing the appropriate anesthetics, analgesics, or tranquilizing drugs during procedures where the animal experienced accompanying pain or distress greater than momentary or slight.

This experimental scenario is necessary for the identification of an antidotal therapy that effectively and safely reduces the maternal and fetal toxicity of organophosphorus (OP) insecticides and improves survival.

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17

4. Species (common name) of animals used in the study.

Hamster

5. Explain the procedure producing pain and distress.

Subsequent to testing efficacy of vaccine candidates in mice, hamsters [the gold standard for Clostridium difficile infection (CDI)] will be used to evaluate vaccine candidates in an effort to develop human therapies for the leading cause of nosocomial antibiotic-associated diarrhea and the etiologic agent of pseudomembranous colitis. Some animals may succumb to the infection prior to an experimental endpoint. A careful monitoring plan and humane alternative endpoints have been included.

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This protocol will evaluate the efficacy of immune based interventions (vaccine and antibody therapies) against CDI. CDI in hamsters is fulminant and almost always rapidly fatal unless treated. Only new therapeutics that show excellent results in mice will be tested in hamsters. Analgesics cannot be used in this work because they mask clinical signs of disease and alter behavior. Clinical signs such as lethargy, depression and hunched posture are critical for determining severity of disease. Survival and rate of recovery are important criteria in efficacy studies of therapeutics. This work will satisfy the need for pre-clinical safety and efficacy data prior to conducting clinical trials in humans.

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46

4. Species (common name) of animals used in the study.

Hamster

5. Explain the procedure producing pain and distress.

Animals are infected with Clostridium difficile and treated with a novel compound. Animals may show signs of infection, i.e., diarrhea. Humane alternative endpoints have been incorporated and moribund animals will be euthanized.

6. Provide the scientific justification for not providing the appropriate anesthetics, analgesics, or tranquilizing drugs during procedures where the animal experienced accompanying pain or distress greater than momentary or slight.

C. difficile infection (CDI) is responsible for at least 30,000 deaths in the United States. This research aims to develop a novel formulation of a repurposed drug for treatment of C. diff. infections. To evaluate the pharmacokinetic profile of this drug, infected animals must be used.

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3. Number of animals used in the study.

21

4. Species (common name) of animals used in the study.

Rabbit

5. Explain the procedure producing pain and distress.

Animals may experience unrelieved pain and/or distress as a result of major morbidity/mortality due to acute radiation sickness. Steps will be taken to minimize pain and/distress among animals including administration of analgesics for pain and humane euthanasia when animals meet the criteria for euthanasia due to major morbidity or upon Veterinary recommendation due to unrelieved pain and/or distress.

6. Provide the scientific justification for not providing the appropriate anesthetics, analgesics, or tranquilizing drugs during procedures where the animal experienced accompanying pain or distress greater than momentary or slight.

The objective of this study is to develop an animal model of acute radiation sickness across the dose range to induce the hematopoietic subsyndrome of acute radiation syndrome to assess the relationship between thrombocytopenia, coagulopathy, and associated vascular etiologies and major morbidity/mortality. Understanding the relationship is critical to future assessment of treatment interventions to save lives in the aftermath of a nuclear and/or radiological accident or attack. While analgesics, anesthetic and/or sedatives will be used to relieve pain and/or distress, it is expected that animals may still experience pain and/or distress considering the endpoint of major morbidity. It is not ethical or feasible to test the efficacy of countermeasures against radiation sickness in humans.

7. 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):

Animal Rule (21 CFR 314.600 through 314.650 - drugs or 21 CFR 601.90 through 601.95 -biological products)

Agency	CFR
U.S. Food and Drug Administration (FDA)	see above

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152

4. Species (common name) of animals used in the study.

Rabbit

5. Explain the procedure producing pain and distress.

Animals undergo different models of hemorrhagic shock and resuscitation. Blood removal is expected to lead to a significant drop in mean arterial pressure, increases in heart rate, and increases in lactate levels. Animals are monitored continuously during the procedure. If blood pressure drops to a point where the animal is in a life-threatening situation or other physiologic events lead to a moribund or life-threatening situation, the animals will be euthanized.

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These experiments are required to determine the efficacy and physiologic impact of a novel blood substitute in a simulated prolonged field care (PFC) setting. Ultimately, the experimental model is designed to mimic a battlefield scenario, with minimal access to care, wherein an individual suffers life threatening blood loss in conjunction with possible critical injury. In order to accurately model this scenario, medical assistance to the animal will be withheld that would otherwise not be available in a PFC setting. All animals will receive analgesia throughout all the protocols, however for a 48- hour protocol, animals will not be sedated.

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16

4. Species (common name) of animals used in the study.

Pig

5. Explain the procedure producing pain and distress.

Post nerve injury, animals will undergo behavioral testing to phenotype the spontaneous and stimulus-evoked behaviors of the animals in response to innocuous and noxious stimuli. During all stimulus-evoked nocifensive testing, animals will be able to maneuver away from the stimulus at any time. In the event that they do not, the stimulus will be removed at a predetermined cutoff time point or intensity level cutoff to avoid tissue damage.

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This study aims to develop and validate a spared nerve injury (SNI)-induced neuropathic pain model. Transcriptomic and protein analyses of pain-relevant tissue from pigs who have undergone SNI surgery will be compared with those that have a sham injury. The results of these analyses will be correlated with the pain behavioral testing data. Since neuropathic pain is a severe and often chronic issue, it is vital that targeted treatments be discovered and/or developed. The stimulus-induced nocifensive responses are a critical component of the study design, as it is necessary to test for neuropathic-related symptoms in order to determine the validity and translational ability of the model. The nocifensive stimuli will be immediately terminated upon a reaction from the pig or if no reaction is

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36

4. Species (common name) of animals used in the study.

Ferret

5. Explain the procedure producing pain and distress.

Animals will be exposed to under-body blast induced hyperacceleration in the absence of anesthesia.

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Exposing animals to blast in the absence of anesthesia is critically important to determine if the animals lose consciousness immediately after the blast or if they show signs of a concussion, e.g., unusual gait or inability to quickly right themselves when placed on their backs. This model reflects what occurs during actual battlefield events at the time injuries occur, i.e., injuries inflicted by Improvised Explosive Devices (IEDs). The complexities of blast injury must be studied in a living animal so that neurobehavioral analysis and histopathological findings can be interpreted following injury to target various treatment options. Analgesia will be provided to animals after exposure to underbody blast, but not before or during.

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