



15 November 2021

Reference: Registration No. 64-R-0001, USDA Annual Report of Research Facility

FY 2021 APHIS Form 7023 Column E Explanation:

- 60 hamsters on SARS-CoV-2 vaccination, challenge, and therapeutic efficacy studies experienced unrelieved pain and/or distress subsequent to virus challenge. The SR IACUC authorized the withholding of analgesics and anti-inflammatories based on the justification provided by the Study Director who stated that the animals which experienced SARS-CoV-2 related illnesses could not be treated with analgesics, as this would mask the clinical indicators of disease indicative of infection, could inadvertently enhance disease progression, and interfere with the viral pathogenesis, thus compromising the scientific integrity of the work. Narcotic analgesics were shown to interfere with the mechanism(s) responsible for interferon production (Geher, W.F. et al., J. Toxicol Environ Health 2:577-582, 1977; Hugh, C.Y. et al., Proc Soc Exp Biol Med 142:106-111, 1973). Moreover, opioids can suppress Natural Killer (NK) cell activity (Berlin, B., et al. Brain Behav Immun 3:129-137, 1989). Also analgesics including buprenorphine can cause histamine release (Marone, G., et al. Int Arch Allergy Immunol 124:249-252, 2001; Stellato, C., Ann NY Acad Sci 406:32-47, 1995). Histamine is a well-known inflammatory mediator and plays a central role in the pathogenesis of allergic and inflammatory diseases by modulating vascular and airway response. To this point, the use of analgesics and antihistamines could hinder the immunological response and pathogenesis to SARS-CoV-2 negating the purposes of this research.



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FY 2021 APHIS Form 7023 Column E Explanation – Nonhuman Primates:

- 4 Cynomolgus macaques (*Macaca fascicularis*), 2 rhesus macaques (*Macaca mulatta*), and 43 African Green Monkeys (*Chlorocebus sabaeus*) on SARS-CoV-2 vaccination, challenge, and therapeutic efficacy studies experienced unrelieved pain and/or distress subsequent to virus challenge. The SR IACUC authorized the withholding of analgesics and anti-inflammatories based on the justification provided by the Study Director who stated that the animals which experienced SARS-CoV-2 related illnesses could not be treated with analgesics, as this would mask the clinical indicators of disease indicative of infection, could inadvertently enhance disease progression, and interfere with the viral pathogenesis, thus compromising the scientific integrity of the work. Narcotic analgesics were shown to interfere with the mechanism(s) responsible for interferon production (Geher, W.F. et al., J. Toxicol Environ Health 2:577-582, 1977; Hugh, C.Y. et al., Proc Soc Exp Biol Med 142:106-111, 1973). Moreover, opioids can suppress Natural Killer (NK) cell activity (Berlin, B., et al. Brain Behav Immun 3:129-137, 1989). Also analgesics including buprenorphine can cause histamine release (Marone, G., et al. Int Arch Allergy Immunol 124:249-252, 2001; Stellato, C., Ann NY Acad Sci 406:32-47, 1995). Histamine is a well-known inflammatory mediator and plays a central role in the pathogenesis of allergic and inflammatory diseases by modulating vascular and airway response. To this point, the use of analgesics and antihistamines could hinder the immunological response and pathogenesis to SARS-CoV-2 negating the purposes of this research.
- 8 rhesus macaques (*Macaca mulatta*) underwent whole body irradiation as a part of an IACUC approved protocol designed to assess the potential of antibiotics as a medical countermeasure to mitigate infection resulting from acute exposure to radiation which could arise in the human population secondary to a radiological or nuclear event, e.g. a "dirty" bomb or nuclear accident. Based on veterinary treatment recommendations, the pain and distress of these animals was mitigated using analgesics, antipyretic agents, food supplements, oral electrolyte supplements, and anti-emetics. The SR IACUC decided that since the pain and distress caused by irradiation and the extent to which that pain and distress was able to be relieved varied, animals undergoing whole body irradiation should be classified into USDA Pain and Distress Category E





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- 131 ferrets (*Mustela putorius furo*) used on an influenza challenge protocol developed clinical illness and are considered to have experienced some degree of unrelieved pain and/or distress secondary to influenza challenge. The withholding of anesthetics and analgesics was approved by the SR IACUC after justification by the Study Director who stated:

"Illness experienced by challenged animals must not be treated with analgesics, as this would compromise the scientific integrity of the study, mask the pathogenesis of the disease, obscure secondary efficacy parameters such as amelioration of clinical signs, could inadvertently accelerate the disease process, and confound the interpretation of euthanasia criteria. Importantly, the use of analgesics could alter the pathogenic and immunologic response to infection, thus making it impossible to interpret the data obtained in this study. Narcotic analgesics were shown to interfere with the mechanism(s) responsible for interferon production (Geher, W.F. et al., J. Toxicol Environ Health 2:577-582, 1977; Hugh, C.Y. et al. Proc Soc Exp Biol Med 142:106-111, 1973). Moreover opioids can suppress Natural Killer (NK) cell activity (Beilin, B., et al. Brain Behav Immun 3:129-137, 1989). Also analgesics including buprenorphine can cause histamine release (Marone, G., et al. Int Arch Allergy Immunol 124:249-252, 2001; Stellato, C., Ann NY Acad Sci 406:32-47, 1995). Histamine is a well-known inflammatory mediator and plays a central role in the pathogenesis of allergic and inflammatory diseases by modulating vascular and airway response. Histamine has been shown to induce activation of human macrophages (Mozzoni, A., et al. J Immunol 170:269-2273, 1999), inhibit interferon alpha release from dendritic cells (Marone, G., et al., Int Arch Allergy Immunol, 124:249-252, 2001) and increase the synthesis and release of IL-10 from human macrophages (Sirois, J., et al. J. Immunol 164:2964-2970, 2000). Clearly, the analgesic-induced release of histamine would directly interfere with the inflammatory process. Studies by Piersman et al, (Lab Anim 33:328-333, 1999) provide an additional example of how analgesics may modify the expression of the disease process. These investigators, using an established murine model of endotoxemia, showed that the opioids fentanyl and buprenorphine directly altered the outcome of their experiments by modulating the immune response. In this case, both opioids caused significant decreases in circulating levels of tumor necrosis factor alpha following administration of lipopolysaccharide (LPS)."