**MPTP Guidelines**

The dopaminergic neurotoxin 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) is frequently used to produce parkinsonism in non-human primates (NHP). The following SOP for the use of MPTP in non-human primates were developed by a subcommittee of the IACUC and approved by vote of the full committee on 11/15/2006.

**Standard Operating Procedures for the use of 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) in nonhuman primates**

**Background:**

Parkinsonism is a devastating brain disorder. Investigations to generate new treatment options for this disorder have a high research priority. Since its introduction in the early 1980s, the MPTP-treated primate has become a ‘gold standard’ model for this disorder.

Systemic injections of MPTP can result in a faithful reproduction of the biochemical and behavioral phenotype of parkinsonism in humans. Unfortunately, it has proven extremely difficult to induce a stable moderately parkinsonian state with this method of treatment. The natural course of parkinsonism after systemic treatment with the toxin is that animals develop severe parkinsonism within 48-72 hours of the injection, which gradually resolves, often leaving the animals virtually normal after several weeks. Individual animals differ greatly in response to the toxin.

One of the attempts to improve upon this situation has been the use of multiple smaller injections of the toxin. While this gives somewhat better control over the animal’s clinical status, the principal problem of recovery and clinical instability remains. Another approach has been the use of more focal lesions of the dopaminergic system with unilateral intracarotid injections of the toxin. This treatment protocol generally results in clinically less invasive parkinsonism. The
disadvantages of this treatment modality are that it may result in some non-parkinsonian features (such as appendicular dystonia), and that near-complete recovery is common in these animals.

These guidelines recognize the scientific value of the MPTP model of parkinsonism, and attempt to address the above-mentioned practical problems associated with the use of this agent.

SOP:

1. Prior to MPTP injections, the animal's baseline weight needs to be determined. The baseline weight is the mean of three consecutive weight measurements, taken while the animal has free access to food, during the two-week period preceding the injections. In young animals, growth-related weight increases must be taken into consideration. Thus, in these animals all weight comparisons after the MPTP treatment must be based on weight projections using nomograms.

2. The dosage requirements for successful MPTP treatments differ greatly between primate species, and may also depend on the age of the animal and other factors. At Emory University, MPTP is most commonly used in Rhesus monkeys. The total daily dose, given by systemic injections or other routes, must not exceed 0.8 mg/kg and the total weekly dose should not exceed 2.5 mg/kg.

3. The use of high cumulative lifetime doses of MPTP needs to be closely coordinated with the veterinary staff. If plans are made to administer MPTP in excess of a cumulative lifetime dose of 15 mg/kg, the veterinary staff needs to be consulted well in advance. The attending veterinarian will then determine whether the animal should be able to tolerate additional MPTP treatments prior to each additional MPTP injection, and whether the investigator needs to seek IACUC approval before additional MPTP doses can be administered.

4. During the acute phase of MPTP effects (i.e., until 72-hours after the last MPTP injection), the care of the animals is supervised by the veterinary staff. Thereafter, the animals are cared for in their normal colony environment. During any of these phases they may need food supplementation or treatment with dopaminergic medications. The need for this is determined through discussions between the veterinary staff and the PI. If supplemental feeding or medication treatments are deemed necessary, it is the PI's
responsibility to arrange for these supplemental feedings or medications to be given by either the veterinary staff or qualified research personnel on the IACUC protocol.

5. All MPTP injections must be documented. At all times, a copy of the documentation must be accessible to the veterinary staff and the research staff. In addition, at Yerkes, this information must be provided to ARS for timely entry into their system. The documentation must include the following information:
   a. The research staff needs to document the clinical state of the animals, and their weight. These records must be updated daily until the state of the animal has stabilized (judged through clinical observations and standardized rating methods), and weekly thereafter.
   b. Food intake charts have to be maintained for at least the first 72 hours after an MPTP treatment. The veterinary staff in consultation with the PI may determine that food intake charts beyond 72 hours are necessary.
   c. Detailed records of medication use. This includes specifics as to the time the medication was given, the type of medication used, the route of administration, the amount given, and side effects of the medications.

6. MPTP-treated animals will be treated with dopaminergic medications (either levodopa or dopaminergic agonists) for as long as they are unable to maintain their weight with no more than 20% weight loss compared to the pre-treatment baseline, or show clear clinical signs of distress such as distress vocalization.

7. If animal is akinetic for greater than a 60 minute block of time in a 24 hour period, dosage of anti-Parkinsonian medication must be adjusted (e.g. by altering administration times, dosages or drugs).

8. Animals judged to be in pain by the vet staff and/or the research staff will be treated with analgesics in addition to the dopaminergic medications mentioned above.

9. The following specific endpoints apply for the use of MPTP in non-human primates:
   a. Weight loss: Animals must be euthanized if they lose more than 25% of their baseline body weight (as defined under item 1).
   b. Anorexia: Anorexia is defined as the inability of the animal to voluntarily consume enough food to maintain its body weight. Animals requiring
mechanically assisted feeding (i.e., tube or gavage feeding) for more than seven continuous days or ten days in a four-week period will be euthanized. If voluntarily accepted by the monkey, syringe feeding can be used for a more extended period of time. Partial supplemental feedings such as high-caloric supplements or the use of primate treats/fruits to maintain the animal’s health are also permissible beyond the 7-day period. Similarly, animals can be maintained beyond the 7-day endpoint if they are able to maintain their weight with the help of dopaminergic medications.

c. If despite the use of anti-Parkinsonian medication, the animal is impaired enough to have extreme difficulty managing normal or everyday situations (e.g. entering or exiting a transfer box or primate chair, interacting with enrichment or personnel, taking medication) for six months (without interruption), the animal needs to be euthanized.

d. Medical conditions repeated or unresponsive to clinical treatment.

10. **Scientific justification must be provided to the IACUC if any of these guidelines cannot be adhered to.**