

## Acute toxicity – MTD/NOAEL studies

**Background:** Development of any new drug involves assessing the benefit-risk balance between the effective therapeutic dose levels and potential side effects and toxicity levels, which may diminish or nullify the curative effects of new molecules. Importance of the early evaluation of toxic properties of drug candidates cannot, therefore, be underestimated. Several types of acute toxicity studies can be done to determine the Median Lethal Dose 50% (LD50), Maximum Tolerated Dose (MTD) or No Observable Adverse Effect Level (NOAEL). The MTD is defined as the dose of a drug that produces an acceptable level of toxicity or the highest dose of a drug that does not cause unacceptable side effects. The NOAEL is the highest level of exposure to the drug at which there are no biologically significant increases in the severity or frequency of adverse effect between the treated animal group and the appropriate control group; some effects which are not considered adverse may be produced at this level. The main objective of the MTD/NOAEL studies in early preclinical stage is to identify optimal range for therapeutic doses to be used in animal efficacy models. These studies also help to identify specific target tissues/organs for toxicity, determine reversibility of toxicity, and identify dosage parameters for repeated-dose toxicity tests.

**Service Details:** A typical protocol includes investigation of 4 escalating doses in “up-and-down” manner after a single dose administration by one or more delivery routes, one of which is the intended route of administration in humans. After administration of the first chosen dose to a group of 6-10 mice or rats (equal number of males/females), animals are observed for 7 days and routinely checked for mortality, morbidity, changes in the body weight and other signs of toxicity. An additional group of animals is then dosed at a higher or lower dose, depending on the presence or absence of signs of toxicity or mortality. The final dosed group of animals is observed for at least 14 consecutive days. One control vehicle-dosed group is included in addition to the four test article-dosed groups. Determination of the signs of toxicity includes general indicators such as mortality, morbidity, body weight as well as terminal blood draws for hematological and clinical chemistry measurements. Gross necropsy is performed on all animals that die and on all survivors at the end of the study.

**Deliverable:** A detailed study report including description of study design, experimental data and interpretation.

**Sample Submission:** Dry compound or compound in pre-made dosing formulation. Amount depends on the toxicity of the test article and study design.