Acute toxicity - LD_{50} study

Background: Development of any new drug involves assessment of 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. Therefore, importance of early evaluation of the toxicity of drug candidates cannot be underestimated. Several types of acute toxicity studies can be done to determine the Median Lethal Dose 50% (LD_{50}), Maximum Tolerated Dose (MTD) or No Observable Adverse Effect Level (NOAEL). The main objective of LD_{50} study is establishing the drug dose which causes death of 50% of the treated animals under the defined conditions of the test. This type of study is usually conducted to help select approximate doses for MTD/NOAEL studies and repeated-dose toxicity tests. The classical method for determining LD_{50} may involve large numbers of animals and has high mortality ratio. Due to such limitations, the LD_{50} test is often replaced by alternative toxicity tests or modified to reduce the number of animals involved. The most frequently used protocols designed with the intention to minimize the number of animals are the fixed dose procedure (FDP) method (OECD 420), the acute toxic category (ATC) method (OECD 436) and the up-and-down (UDP) method (OECD 425). Choice of a particular method depends largely on the expected toxicity of the tested drug and exact goals of the study.

Service Details: We use a modified protocol to approximately estimate LD_{50} levels by “up-and-down” or “staircase” method using a small number of animals. Typical experimental design involves 10 female BALB/c mice or Wistar rats, 5 single dose levels (2 animals per dose), and oral, intraperitoneal or intravenous drug delivery routes. The animals treated with the first selected dose are monitored for signs of toxicity and mortality at the first, second, fourth and sixth hour for toxicity signs. Mortality observed within 24 hours is recorded. Thereafter, depending on the level of tolerance of the first dose, subsequent doses (less than the initial dose, if not well tolerated or greater than the initial dose, if well tolerated) are administered to the animals in groups of two to six, depending on the balance adjustment between minimizing the number of animals sacrificed and precision of LD_{50} calculations. They are observed daily for additional 7 days for signs of delayed toxicity. The percentage mortality values are converted into LD_{50} values by Probit Analysis. Standard service also includes the final gross necropsy 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.