

# Lead Optimization Toxicology

Pharmaceutical and biotech companies are often faced with seemingly insurmountable challenges in developing new drugs. Even after the successful identification of an active molecule against a disease target, many drugs fail to ever reach the market because of unacceptable toxicity.

Charles River is committed to providing services which best support the drug discovery and lead selection processes. By elucidating possible safety concerns earlier in the drug development process, our lead optimization toxicology service allows researchers to bring forward candidates that are more likely to succeed in preclinical testing.

Lead optimization toxicology study types are typically offered within Charles River at three levels of increasing complexity. However, this approach can be customized according to the class of compound and therapeutic target. Using an efficient design, studies can be tailored to meet the testing paradigm of your lead candidate selection program.

Quick study initiation, conduct, and reporting are made possible through simple modular protocols that are preapproved by our global IACUC, a dedicated supply of rodents from our Research Models division, the immediate availability of our nonrodent colonies, and by preformatted report templates.

## Program

- Multilevel study designs
- Modular preapproved protocols
- Rodent and nonrodent species
- Variety of dose routes
- Analytical chemistry
- Clinical chemistry
- Pathology
- Toxicokinetics
- Preformatted reports

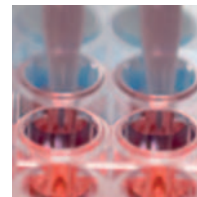
## Discovery Services

- *In vitro* ADMET
- Formulation development
- Pharmacokinetic/ADME screening
- Pharmacology
- Lead optimization toxicology
- Small animal imaging
- Oncology services
- Biomarker analysis
- Bioanalysis
- Phenotyping services



## Lead Optimization Toxicology Study Types

Level I Initial Screening	Level II Toxicity Profiling	Level III Candidate Selection
<b>General Design</b> 1- to 4-day rodent studies One or multiple analogs compared 3 to 6 per group – one sex Screening objective	Up to 14-day rodent studies Multiple dose levels 5 to 6 per group – one or both sexes	2- to 3-week custom pilot studies Large animal (at least 2/sex/group) At least 2 dose levels and/or increased number of rodents – both sexes
<b>Results</b> Vehicle suitability Intrinsic toxicity Limited pathology Clinical chemistry Hematology Exposure	Quantify toxicity at multiple levels Pathology Clinical chemistry Hematology Limited toxicokinetic profile	Establish margin of safety Toxicity limits Pathology Clinical chemistry Hematology Full toxicokinetic profile
<b>Goal</b> Screen many potential analogs Rapid throughput Abbreviated report	Multilevel or analog series Abbreviated report	Lead candidate selection for next stage Custom reporting



### Level I

Level I studies provide high-throughput for a significant number of molecules in rodent assays where early toxicity and exposure information is needed. Study types include range finding, single level comparisons, and early multilevel designs. Exposure can be established by collecting blood samples just prior to termination, and gross necropsy provides limited target tissue identification. These designs allow rapid screening of a large number of analogs and provide information to aid combinatorial chemistry work.

### Level II

Level II rodent studies give a more complete profile of multiple candidates at several dose levels. These studies provide information on toxicity and tissue pathology as it relates to dose level. Limited toxicokinetic samples may be collected from the primary test group, or a full curve evaluation may be obtained from satellite groups. This design provides a better understanding of toxicity at multiple dose levels and target tissue effects, which assists in identifying the best candidates for further development.

### Level III

This stage is designed to assist you in the final evaluation of a test article by providing a full picture of the toxicology and pathology associated with the individual drug development candidate before moving into traditional preclinical GLP testing. These pilot toxicity studies are conducted in rodent and/or nonrodent species, depending on your needs.