Contract Concept: Genetic Toxicology Testing in Support of NTP

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Overview

An assessment of genotoxicity potential is a critical component of the comprehensive toxicological characterization of a substance, due in large part to the mechanistic linkage between genetic damage and a number of defined adverse health outcomes including cancer, neurodegenerative disease, birth defects, and somatic mutational load. Thus, the objective of this contract is to continue a decades-long effort to provide the NTP with the capability to characterize the genetic toxicity potential of thousands of compounds of interest to the Program using a variety of *in vitro* and *in vivo* methods. The testing approaches proposed in this concept include a mix of traditional, well-characterized assays such as, for example, the bacterial mutation assay (Ames assay) and the *in vivo* peripheral blood rodent micronucleus (MN) assay, as well as new molecular approaches that provide enhanced understanding of mechanism of action and quantification of the low end of the dose-response curve for determining benchmark doses/points of departure to support refined risk assessment. The protocols used for the traditional assays are governed by international testing guidelines (OECD) and the data generated are accepted by regulatory agencies such as the FDA and EPA as valid measures of genotoxicity. The newer molecular approaches, some of which are still in early stages of development, will be used as adjuncts to traditional assays to provide clarifying data, while the genetic toxicology community works to achieve international harmonization of protocols. All testing under this contract will be conducted in a manner consistent with Good Laboratory Practice guidelines.

Consistent with the 3-Rs concept (Refinement, Replacement, Reduction) in animal testing, all *in vivo* assays that are proposed for this contract can be integrated into ongoing toxicology studies, thus eliminating the need for independent tests in most instances. In addition, because the proposed *in vivo* assays (e.g., MN and comet assays) can use peripheral blood as a sample source, they also can be used in human translational studies, a capability that the NTP has employed in the past to investigate cytogenetic effects in humans following observations in NTP animal studies.

Proposed Changes to the Current Statement of Work:

The proposed Statement of Work (SOW) will include all current capabilities for conducting genetic toxicology studies and will be revised to include additional capabilities for generating detailed molecular data to better define mode of action and low-dose effects, as well as provide means of early detection of mutational changes *in vivo* that are consistent with known toxicological endpoints (e.g., cancer driver mutations).