## Moving Beyond Animal Data as the Gold Standard

**Presenter:** Dr. Nicole Kleinstreuer, NIEHS/DNTP

Developing more human-relevant methods to safety testing, and establishing scientific confidence in those methods, is one of the fundamental objectives of the strategic roadmap. However, existing safety testing frameworks rely almost exclusively upon animal tests, whose reliability and relevance to human toxicity have not been fully characterized. As much of the legacy in vivo data that we have relied upon for decades becomes digitized and computationally accessible (initially through arduous manual efforts and slowly via automated natural language processing systems under development), opportunities arise to assess the true variability and inherent uncertainty in the animal studies. These analyses (on bioassays such as the rodent uterotrophic and Hershberger endocrine-relevant tests, the murine local lymph node assay for skin sensitization, and the acute oral LD50 test for systemic toxicity) reveal that the agreement within the same type of high-quality guideline-like studies run independently on the same chemicals is only in the range of 70-80% concordance. The inherent variability observed in these tests, despite controlling for study protocol factors, can help to appropriately set expectations for the performance of new non-animal approaches when compared to these reference data.

In areas such as skin sensitization, where human clinical data are available as a basis for comparison, there is strong evidence that mechanistically driven testing strategies linked to the skin sensitization adverse outcome pathway (AOP) outperform the animal tests in predicting human sensitization potential. This leads to the hypothesis that other non-animal approaches, which are designed to target human biology-based AOPs, may in fact be superior to the animal tests even when their predictive performance against reference animal data appears sub-par. A pertinent example of this concept occurs in the field of eye irritation testing, where the Draize rabbit eye test demonstrates poor reproducibility and questionable human relevance. Therefore, rather than attempting to predict hazard categories based on rabbit eyes, effects observed in vitro on human corneal epithelial cells may present a more compelling case for human relevance. Outside of topical toxicity applications, predicting systemic and internal organ toxicities, human disease research, and drug discovery programs, among others, may also benefit from human-relevant pathway-based approaches that are both computational and experimental in nature.