SOT Session Proposal

PRESENTATION TYPE: Workshop
SECONDARY PRESENTATION TYPE: Symposium

SESSION TITLE:
Read-across - At a crossroads of regulatory science and informatics: Is there scope to exploit QSAR principles to inform read-across development and evaluation

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Role: Presenter
Member Type: (Non-member)
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Presentation Title: Quantifying uncertainty in read-across assessment – an algorithmic approach
Presentation Description:
Read-across is a popular data gap filling technique within category and analogue approaches for regulatory purposes. Acceptance of read-across remains an ongoing challenge with several efforts underway for identifying and addressing uncertainties. Here we demonstrate an algorithmic, automated approach to evaluate the utility of *in vitro* bioactivity data ("bioactivity descriptors", from EPA's ToxCast program) and chemical descriptor information to derive local validity domains (specific sets of nearest neighbors) to enable read-across of toxic effects observed in typical in vivo study types. The performance of the read-across prediction was evaluated in two ways. A receiver operating characteristic (ROC) analysis of the predicted toxicity and experimental toxicities is conducted for *k* nearest neighbors (where the value of *k* ranged from 1 to the maximum number of chemicals in the neighborhood), and with a similarity threshold, *s* (where the value of *s* ranged from the minimum to maximum values of s across all unique pairwise comparisons in the neighborhood). The area under the curve (AUC) is taken as a measure of performance for a given *k* and *s* value. In addition, the overall performance across all values of *k* and *s* in a local neighborhood is summarized as the volume under the surface (VUS) of the ROC scores. The latter allows a comparison across different toxicities to be made across the entire neighborhood to determine for which effects, bioactivity or chemical descriptors gave rise to predictions with greater or lesser confidence. Here we present case studies demonstrating the utility of these metrics to evaluate read-across performance as well as improvements in performance when toxicokinetic information is taken into account.
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