New Approach Methodologies: Computational Tools

- **The Future of Computational Toxicology: Balancing Machine Learning and Mechanistic Modeling**

  Presenter: Dr. Nicole Kleinstreuer, NIEHS/NTP

  Advances in computational tools now provide unprecedented access to collecting, curating, and analyzing large datasets, enabling models built using artificial intelligence and machine learning that deliver predictions across the chemical universe. Such machine learning approaches are often contrasted against mechanistic models based on detailed biological knowledge. ICCVAM and NICEATM have invested substantial resources towards developing machine learning and computational methods to address problems in predictive toxicology, from automating the identification of high-quality reference data to global crowdsourcing approaches to model adverse health outcomes such as endocrine disruption and acute systemic toxicity. Simultaneously, work is ongoing to construct and refine mechanistically driven tools and models. Effective computational toxicology approaches should leverage both machine- and mechanism-based strategies, both of which rely heavily upon reliable, curated, annotated datasets such as those contained in the Integrated Chemical Environment (ICE: https://ice.ntp.niehs.nih.gov/). Current efforts to add data structure through controlled vocabularies and expert groupings can make data more accessible, particularly for users without in-depth knowledge of test systems, and tools such as the in vitro to in vivo extrapolation (IVIVE) workflow aid in interpretability. Feedback will be requested from SACATM on the ongoing developments in ICE, planned expansion of the IVIVE tool, and opportunities for mechanistic and machine learning models to inform predictive toxicology.

- **Collaborative Acute Toxicity Modeling Suite (CATMoS)**

  Presenter: Dr. Kamel Mansouri, Integrated Laboratory Systems, Inc.

  The importance of assessing chemicals for acute oral systemic toxicity potential (LD50), the lack of available *in vitro* approaches, and the availability of existing LD50 data for a broad range of chemicals encourage the use of *in silico* models as an alternative to predict acute oral toxicity and bridge data gaps. NICEATM and the ICCVAM Acute Toxicity Workgroup organized an international collaborative project to develop *in silico* models for predicting acute oral toxicity. In total, 35 groups participated, submitting 139 predictive models built using a dataset of 11,992 chemicals. Models were developed for five endpoints: LD50 value, EPA hazard categories, GHS hazard categories, very toxic (LD50 < 50 mg/kg), and non-toxic (LD50 > 2000 mg/kg). Predictions within the applicability domains of the submitted models were evaluated using external validation sets, then combined into consistent consensus predictions based on a weight-of-evidence approach, forming the Collaborative Acute Toxicity Modeling Suite (CATMoS). The resulting consensus model leverages the strengths and overcomes the limitations of individual modeling approaches. The consensus predictions are fully reproduceable and performed at least as well as the *in vivo* acute oral toxicity assay in terms of accuracy. The CATMoS consensus model is available via the free and open-source tool OPERA (https://github.com/NIEHS/OPERA),

which also provides predictions for various physicochemical and toxicological endpoints with applicability domain assessments and accuracy estimates. CATMoS predictions for the ~850k chemical structures in DSSTox will ultimately be publicly accessible via NTP's Integrated Chemical Environment (ice.ntp.niehs.nih.gov) and the EPA's CompTox Chemicals Dashboard (comptox.epa.gov/dashboard).

- **New Approach Methodologies for Exposure from EPA's ExpoCast Project**

  Presenter: Dr. Kristin Isaacs, U. S. Environmental Protection Agency

  Exposure is a key component of evaluating the risks posed by anthropogenic chemicals. Exposure is the degree or contact between a chemical and human and ecological target populations. EPA's Exposure Forecaster (ExpoCast) project is charged with the development of new datasets and predictive models that provide exposure information for thousands of chemicals to support agency decision-making. ExpoCast datasets enable the development of cheminformatic machine learning models that fill critical gaps for data-poor chemicals and parameterize new mechanistic models for human, ecological, and occupational exposure pathways. These pathway models can be statistically integrated with available monitoring data to produce consensus exposure predictions and estimates of uncertainty. New high-throughput analytical approaches are also being developed that will expand the chemical space monitored in human and ecological media. Finally, new high-throughput toxicokinetic data and models are used to link ExpoCast exposure predictions to *in vitro* hazard data. These ExpoCast tools, which can be considered New Approach Methodologies for exposure, are suitable for dealing with the thousands of chemicals in commerce with limited sources of chemical exposure information.