Presentation Abstracts and Background Materials

SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS

Session 4: Computational Resources
Thursday, September 3, 2020

➢ ICE (Integrated Chemical Environment) & In Vitro to In Vivo Extrapolation (IVIVE)

Presenter: **Dr. Shannon Bell, ILS**

The Integrated Chemical Environment (ICE) is a web-based resource for data and tools to support development and evaluation of new, revised, and alternative methods. In this presentation I will provide an overview of ICE, the data in ICE and ICE tools. A case study will be presented on the online in vitro to in vivo extrapolation (IVIVE) tool that allows users to generate predictions of in vivo exposures needed to generate the observed in vitro bioactivity. As part of the case, our recent efforts in mapping data to improve accessibility and interpretation of high throughput screening assays will be described. Plans for meeting FAIR (findable, accessible, interoperable, and reusable) data principles and upcoming ICE tool enhancements will be presented.

Background

- An Integrated Chemical Environment to Support 21st-century Toxicology
- An Integrated Chemical Environment with Tools for Chemical Safety Testing
- ICE Webpage: https://ice.ntp.niehs.nih.gov/

➢ Collaborative Modeling Project for Predicting Acute Oral Toxicity (CATMoS)

Presenter: **Dr. Kamel Mansouri, ILS**

In order to fulfill the pressing need to accurately assess chemicals for acute oral toxicity potential, NICEATM and the ICCVAM Acute Toxicity Workgroup organized the Collaborative Acute Toxicity Modeling Suite (CATMoS) project to develop in silico models as alternatives to predict LD50 and bridge data gaps. Participants from 35 international groups submitted a total of 139 predictive models built using a dataset of 11,992 chemicals split into training (75%) and evaluation sets (25%). Crowdsourced models were developed for five endpoints identified as relevant to regulatory decision frameworks: 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, then combined into consensus predictions based on a weight-of-evidence approach. The resulting consensus model, forming the CATMoS Suite, leverages the strengths and overcomes the limitations of individual modeling approaches. The consensus predictions are fully reproduceable and performed at least as well as independent replicate in vivo acute oral toxicity assays. The CATMoS consensus model can be applied to any new chemical via a k-nearest neighbors approach and is available via the free and open-source tool OPERA (Open Structure-activity/property Relationship App). OPERA is a comprehensive standalone suite of QSAR models including chemical structure standardization workflow and molecular descriptor processing. In addition to predictions for physicochemical properties, pharmacokinetic and toxicological endpoints, OPERA also provides applicability domain and accuracy assessments (https://github.com/NIEHS/OPERA). CATMoS predictions processed by OPERA for the ~850k chemical structures in DSSTox are made publicly accessible via NTP's Integrated Chemical Environment and subsequently at the EPA's CompTox Chemicals Dashboard.

Background

- Predictive Models for Acute Oral Systemic Toxicity: A Workshop to Bridge the Gap from Research to Regulation
- OPERA Models for Predicting Physicochemical Properties and Environmental Fate Endpoints
- Status of Acute Systemic Toxicity Testing Requirements and Data Uses by U.S. Regulatory Agencies

➢ Toxicokinetic and Toxicological Risk Mapping

Presenter: **Dr. Kyle P. Messier, NIEHS/DNTP**

We propose a novel interdisciplinary framework for merging geospatial exposure science with toxicological dose-response modeling that produces an alternative approach to environmental and human health risk mapping. Most importantly, this framework provides an intuitive and translatable outlet for understanding the human health risk posited from in-vivo and in-vitro toxicological studies through the use of geospatial maps.

The framework relies on a geospatial (or spatiotemporal) exposure assessment that follows traditional exposure assessment approaches such as land-use regression or machine learning. The exposure assessment is routed through toxicokinetic models to produce an internal dose concentration in blood or target organ that is in units comparable to those used in toxicological dose-response studies. The internal dose estimates are then compared to in vivo or in vitro dose-response estimates such as the half-maximal activity concentration (AC_{50}) or inhalation reference concentration (RfC). A work-in-progress case study of volatile organic compound air concentrations from across the United States will be included as a demonstration of the new framework..

Background

- Completing the Link Between Exposure Science and Toxicology for Improved Environmental Health Decision Making: The Aggregate Exposure Pathway Framework