New Approach Methodology Use for Regulatory Application

Tools for Computational Toxicology
Hands-On Training in Computational Methods
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ABSTRACTS

OPERA: Open access tools for toxicity and phys-chem property predictions Kamel Mansouri, Integrated Laboratory Systems, Inc.

Kamel Mansouri
Integrated Laboratory Systems, Inc.

OPERA is a free and open-source/open-data suite of QSAR models providing predictions on physicochemical properties, environmental fate, and toxicity endpoints. All OPERA models were built on curated data and standardized QSAR-ready chemical structures. Recent additions to OPERA include models for:

- Estrogenic activity from the Collaborative Estrogen Receptor Activity Prediction Project (CERAPP)
- Androgenic activity from the Collaborative Modeling Project for Androgen Receptor Activity (CoMPARA)
- Acute oral systemic toxicity from the Collaborative Acute Toxicity Modeling Suite (CATMoS)

Other endpoints predicted by OPERA models include:

- physicochemical parameters such as octanol-water partition coefficient (logP), octanol-water dissociation coefficient (logD) and the dissociation constant (pKa)
- Parameters for inputs into pharmacokinetic models, such as hepatic clearance and plasma binding
- Ecotoxicity parameters such as fish bioconcentration factor, soil adsorption coefficient, and biodegradability

OPERA predictions of toxicity and physicochemical properties are available through the EPA Comptox dashboard and the Integrated Chemical Environment (ICE). For local use, the OPERA application can be downloaded from the NIEHS GitHub repository. Command-line and graphical user interface versions are available for Windows and Linux operating systems.

Regulatory submission of (Q)SAR models to support ICH M7 and other guidelines

Glenn Myatt
Leadscope, Inc.

This presentation will review several methods and frameworks developed by Leadscope to support the use of (Q)SAR models as part of regulatory submissions. One such regulatory application is the International Council for Harmonization (ICH) M7 guideline for pharmaceutical impurities. This guideline recommends the use of two complementary (Q)SAR models (expert rule-based and statistical-based) to predict bacterial mutagenicity. Both methodologies will be reviewed along with strategies to conducting an expert review of the results. A particularly challenging issue arises when the (Q)SAR models generate out-of-domain and/or indeterminate results. This presentation will describe recent work that quantifies the risk of missing a mutagenic impurity based on different outcomes from the (Q)SAR models.

DEREK software for toxicity prediction Maggie Coombs, Lhasa, Ltd.

Maggie Coombs
Lhasa, Ltd.

Lhasa Limited develops in silico tools for the toxicological assessment of chemicals and acts as an honest broker in data sharing projects. Lhasa tools can be used to assist in regulatory submissions under ICH M7 and RDC 53 guidelines through decision support, weight of evidence, and read across. This utility of Lhasa products in different use cases will be demonstrated.

UL Cheminformatics Toolkit - a web application for chemical hazard estimates

Tom Luechtefeld
InSilica

Chemical data is growing at an exponential pace, with tens of thousands more kinds of tests and millions more chemicals tested per year. However, most chemical property models focus on narrow domains and fail to leverage the vast majority of available data. Neural networks enable transfer learning where models trained on one task accelerate learning on other tasks. We show transfer learning models result in accuracy improvements across a variety of chemical endpoints. The UL Cheminformatics Tool Kit models 74 different chemical endpoints including acute oral-, dermal- and inhalation- toxicity, dermal sensitisation, dermal- and eye-irritation, genotoxicity, and acute- and chronic-aquatic toxicity. In this presentation we will discuss transfer learning, and the large multi-task neural network powering the UL cheminformatics toolkit.