Presentation Abstracts and Background Materials

SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS

Session III: NICEATM Computational Resources
Friday, September 22, 2023

The Integrated Chemical Environment (ICE): Open-access Tools to Support Chemical Evaluations

Presenter: Ms. Victoria Hull, Inotiv

In an effort to provide user-friendly access to high quality data and computational tools that explore and support new approach methodologies (NAMs), NICEATM has developed the Integrated Chemical Environment (ICE; https://ice.ntp.niehs.nih.gov/). This presentation will provide an overview of the intended uses of ICE and briefly introduce ICE data and its suite of interoperable tools. Examples will be presented to show how these tools can be used to identify structurally similar chemicals, explore high-throughput sequencing assays, predict tissue concentrations, relate in vitro measurements to in vivo equivalent administered doses, and characterize chemical use categories. Recent updates made to these features in release 4.0 and subsequent mini releases will also be highlighted. This includes, but is not limited to, the integration of population-level exposure predictions from EPA's SEEM3 model, new gestational models from EPA's httk package, the ability to search through chemical synonyms, updated datasets, and a beta-stage Query Summary option that provides summary and endpoint-specific visualizations. The presentation will also briefly highlight a generalized workflow under development to incorporate pathway-related variability for select Phase I CYP and Phase II UGT enzymes into PBPK models. This workflow will eventually be incorporated into ICE. Feedback from this presentation will be used to focus future efforts on ICE feature development.

Background

- Abedini et al. Application of new approach methodologies: ICE tools to support chemical evaluations. https://doi.org/10.1016/j.comtox.2021.100184
- Unnikrishnan et al. Integrated Chemical Environment: an advanced platform aiding NAM-based chemical assessments. https://ntp.niehs.nih.gov/sites/default/files/iccvam/meetings/sot23/sot2023-unnikrishnan-poster.pdf

OPERA: Open-Source QSAR Models for Regulatory Support

Presenter: Dr. Kamel Mansouri, NIEHS

OPERA is a suite of over twenty QSAR models that assess toxicity endpoints and various properties. It follows OECD principles and is freely accessible, based on open-source/open-data. OPERA offers high accuracy models with minimal complexity, supporting mechanistic interpretation when possible. The models are built on curated experimental data and standardized QSAR-ready chemical structures.

New additions to OPERA include models for ADME parameters like fraction unbound to plasma protein (Fu), hepatocyte intrinsic clearance (Clint), and Caco2 permeability (logPapp). It also includes consensus models for predicting estrogen and androgen pathway activity and acute oral systemic toxicity. In the latest version, OPERA models were updated with the latest publicly available datasets, improving their predictivity and applicability domain coverage. It can generate predictions for single chemicals or in batch mode and accepts chemical structure inputs through its internal QSAR-ready standardization workflow or via structure identifiers from its database. Prediction reports with accuracy estimates, applicability domain assessments, and more are provided.

OPERA predictions are accessible through EPA's CompTox Chemicals Dashboard, the National Toxicology Program's Integrated Chemical Environment, and FDA's Precision Platform. OPERA can be downloaded as a standalone command-line or graphical user interface for Windows and Linux. It can also run as a plugin within the OECD's QSAR Toolbox and is provided as Python, C/C++, and Java libraries for integration into other applications. *The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of any federal agency*.

Background

- Mansouri et al. OPERA models for predicting physicochemical properties and environmental fate endpoints. https://doi.org/10.1186/s13321-018-0263-1
- Mansouri et al. CERAPP: Collaborative Estrogen Receptor Activity Prediction Project. https://doi.org/10.1289/ehp.1510267
- Mansouri et al. CoMPARA: Collaborative Modeling Project for Androgen Receptor Activity. https://doi.org/10.1289/EHP5580
- Mansouri et al. CATMoS: Collaborative Acute Toxicity Modeling Suite. https://doi.org/10.1289/EHP8495

Web Application to Predict Skin Sensitization Using Defined Approaches

Presenter: Dr. Kim To, Inotiv

Skin sensitization is a critical regulatory toxicity endpoint associated with allergic contact dermatitis. Defined approaches for skin sensitization (DASS) have been developed to identify potential skin sensitizers by integrating non-animal test methods that represent key events in the skin sensitization adverse outcome pathway. We developed the DASS App, an open-source web application, to facilitate user application of four defined approaches that have been accepted by the OECD or U.S. Environmental Protection Agency. The DASS App enables users to implement non-animal approaches to evaluate chemical skin sensitization without the need for additional software or computational expertise. The app supports upload and analysis of user-provided data, includes steps to identify inconsistencies and formatting issues, and provides hazard predictions in a downloadable format. The DASS App is available on the National Toxicology Program website at https://ntp.niehs.nih.gov/go/40498.

This presentation will provide background information about the DAs, followed by a demo of the web application.

Background

- To et al. DASS App: integrating data from non-animal test methods to predict skin sensitization hazard and potency. https://doi.org/10.33774/coe-2023-z56nq

ChemMaps.com v2.0 – Exploring the Environmental Chemical Universe

Presenter: Dr. Alex Borrel, Inotiv

Access to computationally based visualization tools to navigate chemical space has become more important due to the increasing size and diversity of publicly accessible databases and associated compendiums of high-throughput screening (HTS) and other descriptor and effects data. Construction of such tools relies on complex projection techniques using molecular descriptors. However, application of these techniques requires advanced programming skills that are beyond the capabilities of many stakeholders. Inspired by the popular Google Maps application, we developed the ChemMaps.com webserver (https://sandbox.ntp.niehs.nih.gov/chemmaps/) to easily navigate chemical space. The chemical space of ChemMaps.com v2.0, released in 2022, adds to this data on approximately one million environmental chemicals from the U.S. Environmental Protection Agency's Distributed Structure-Searchable Toxicity (DSSTox)

inventory. ChemMaps.com v2.0 incorporates mapping to HTS assay data from the U.S. federal Tox21 research collaboration program, which includes results from approximately 2,000 assays tested on up to 10,000 chemicals. This presentation will showcase examples of how ChemMaps.com can be utilized for read-across analysis, risk assessment, and exploring properties of poorly characterized chemicals such as per- and polyfluorinated substances (PFAS).

Background

- Borrel et al. Exploring drug space with ChemMaps.com. https://doi.org/10.1093/bioinformatics/bty412
- Borrel et al. ChemMaps.com v2.0: exploring the environmental chemical universe. https://doi.org/10.1093/nar/gkad380