Interagency Coordinating Committee on the Validation of Alternative Methods

Presentation Abstracts and Background Materials

SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS

Session 2b: Ecotoxicology Testing: Research Application
Tuesday, September 28, 2021

CATMoS: Acute Oral Toxicity Predictions for Environmental Safety Assessment

Presenter: Dr. Kamel Mansouri, National Institute of Environmental Health Sciences

To address the pressing need to rapidly and accurately assess the safety of environmental chemicals and bridge data gaps, NICEATM and the ICCVAM Acute Toxicity Workgroup organized a global collaborative project to develop predictive in silico models of acute oral systemic toxicity potential. Participants from 35 international groups submitted a total of 139 models built using a dataset of 11,992 chemicals split into training (75%) and evaluation (25%) sets. These 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 and combined into consensus predictions based on a weight-of-evidence approach. The resulting Collaborative Acute Toxicity Modeling Suite (CATMoS) leverages the strengths and overcomes the limitations of individual modeling approaches. The consensus model predictions are fully reproducible and demonstrated equivalent performance to independent replicate in vivo acute oral toxicity assays. To generate consensus predictions for new chemicals, CATMoS is implemented in the free and open-source tool OPERA (Open Structure-activity/property Relationship App), a comprehensive standalone suite of QSAR models including a chemical structure standardization workflow and molecular descriptor processing, in addition to applicability domain and accuracy assessments. CATMoS predictions processed by OPERA for the DSSTox library of ~850k chemical structures are made publicly accessible via NTP's Integrated Chemical Environment (https://ice.ntp.niehs.nih.gov/).

CATMoS predictions are currently being evaluated by different regulatory agencies for potential use as alternative in the risk assessment process. EPA has specifically curated LD50 data for a list of over 100 chemicals derived from previous regulatory studies to assess the usability of CATMoS predictions for environmental chemical safety assessment. Preliminary results show that CATMoS consensus predictions are either overlapping or more conservative than the existing LD50. This analysis also highlights variability and conflicts between different sources of animal LD50 data. This ongoing study will be detailed in a manuscript that will be available as soon as the results are finalized. *This abstract does not necessarily reflect NIEHS or EPA policy*

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 Used by U.S. Regulatory Agencies

- Collaborative Acute Toxicity Modeling Suite (CATMoS)
- OPERA Links:
  - https://github.com/NIEHS/OPERA
  - https://ntp.niehs.nih.gov/go/opera
- NTP/ICE Links:
  - https://ice.ntp.niehs.nih.gov/Search
- ICCVAM Strategic Roadmap

The Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) Tool: Catalyzing a Change in Species Extrapolation

Presenter: Dr. Carlie Lalone, U.S. Environmental Protection Agency

The Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) tool v1.0 was released publicly in 2016 and has since evolved to incorporate a number of new features for rapid synthesis and evaluation of protein conservation across species to predict chemical susceptibility. The SeqAPASS tool has been applied to challenges in species extrapolation surrounding pesticide and pharmaceutical susceptibility, extrapolation from high throughput screening results, defining the taxonomic domain of applicability for adverse outcome pathways, prediction of bioaccumulation potential, and research hypotheses generation. Examples demonstrating the utility of the SeqAPASS tool toward current regulatory challenges have accompanied new version releases and been described in multiple publications. SeqAPASS v5.0 has been released with a decision summary report that combines evidence of conservation from primary amino acid sequence, functional domain(s), and critical amino acid comparisons. Current development efforts have advanced toward protein structure creation and similarity comparisons across species, to add a line of evidence of chemical-protein interactions across species. The SeqAPASS tool is the first of its kind to be developed specifically for researchers and decision-makers to extrapolate toxicity knowledge across 100s-1000s of untested organisms in a consistent, transparent, and publicly accessible pipeline using state-of-the-science techniques in bioinformatics. The tool has catalyzed the use of protein sequence information in decision-making and has been recognized in the *Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption* as a useful tool to address challenges in cross species extrapolation. This presentation will describe the SeqAPASS tool, several examples of how it has been applied, and the path forward for continued development and integration in decision-making scenarios.

Background

- Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS): A Web-Based Tool for Addressing the Challenge of Cross-Species Extrapolation of Chemical Toxicity
- Evidence for Cross Species Extrapolation of Mammalian-Based High-Throughput Screening Assay Results
- Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization
- High-Throughput Transcriptomics Platform for Screening Environmental Chemicals

- Sequence Alignment to Predict Across Species Susceptibility