NICEATM computational tools and resources supporting alternative test method development and evaluation

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OBJECTIVES

- Increase data availability for development and evaluation of new approach methodologies (NAMs).
- Provide accessible computational tools that can be used to support NAMs.
- Increase accessibility of assays, data, and methods for those with limited computational resources or expertise.

APPROACH

- Identify, curate, and annotate data sets.
- Develop multiple methods of access.
- Integrate data sets and their metadata with models that support computational toxicology approaches for users of all expertise levels.

MAIN RESULTS

- NICEATM has two free and open-source tools that support computational toxicology approaches:
  - Integrated Chemical Environment (ICE)
    - Web platform for accessing data and tools
  - OPEn structure–activity/property Relationship App (OPERA)
    - Suite of QSAR models

Integrated Chemical Environment

OPERA OPEn saR App

IMPACT

- ICE tools and data are freely available to all.
- OPERA models and predictions are being used by multiple government agencies and other stakeholders.
- **For more information, contact:** Jaleh A. Abedini, jabedini@ils-inc.com

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OBJECTIVES

- NICEATM supports the development and evaluation of new, revised, and alternative methods for implementing new approach methodologies (NAMs) for chemical safety.
    - In order to advance non-animal tests and be able to develop, evaluate, and implement new methods for chemical evaluation, we require access to reliable data and tools.
    - NICEATM seeks to provide access to reliable data and tools via easy-to-use graphical web interfaces and open-source software.
    - NICEATM tools provide data to users in computationally friendly format**,** and tools are accessible to non-subject matter experts.
    - Extensive data curation ensures that users can retrieve, integrate, and analyze data that is trustworthy and ready to use.

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APPROACH

- NICEATM identifies, generates, curates, and annotates relevant data sets. These include:
  - In silico data and parameter predictions generated using computational models.
  - In vivo and in vitro data from publications, publicly available databases, and/or validation studies.
  - Chemical lists based on reference standards, agency classifications, and common libraries.
  - ToxCast and Tox21 HTS data, curated by NICEATM to:
    - Improve the robustness of calls.
    - Add additional context to the data through mapping to the assays to mechanistic targets and modes of actions using National Cancer Institute's standardized terminology.

- Data adhere to FAIR (Findable, Accessible, Interoperable, and Reusable; https://www.go-fair.org/fair-principles/) data principles. Adherence to these principles improves utility of these data and tools.

- NICEATM provide multiple methods of data access and interaction:
  - Ability to merge datasets on common chemicals.
  - Integration of data with computational models.
  - Interactive computational tools.
  - Open-source software.
  - Easy-to-use graphical web interfaces.
  - Supports users of all expertise levels.

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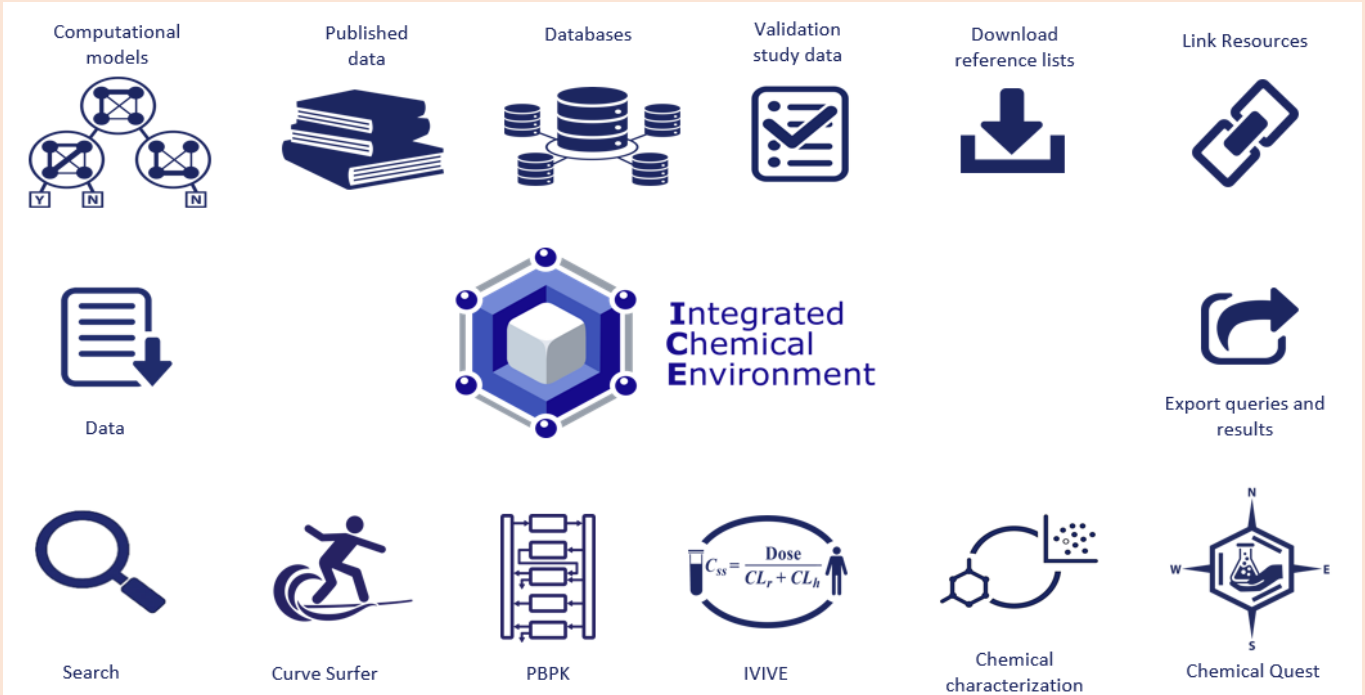
MAIN RESULTS: INTEGRATED CHEMICAL ENVIRONMENT (ICE)

- ICE offers interactive computational tools that can characterize and predict toxicity for user-defined chemicals.
- ICE tools support:
  - Data integration: bring together data from multiple sources.
  - Dynamic results exploration providing publication-quality graphics.
  - Data analysis and characterization using workflows.
  - Data portability: ICE connects with other tools
    - EPA CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard)
    - NTP Chemical Effects in Biological Systems (CEBS: https://manticore.niehs.nih.gov/cebssearch)



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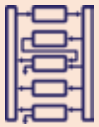
MAIN RESULTS: INTEGRATED CHEMICAL ENVIRONMENT (ICE)

- **ICE Search**
  - Search data by toxicity endpoint, common chemical lists, and/or user-defined chemicals.

- **Curve Surfer**
  - View concentration-response curves for ICE curated high-throughput screening (cHTS) data.



- **PBPK***
  - Generate predictions of tissue-specific chemical concentration profiles following a dosing event.

- **IVIVE***
  - Estimate in vivo equivalent administered dose (EAD) corresponding to in vitro activity concentrations.

- **Chemical Characterization**
  - View and compare chemical properties and product uses (US EPA CPDat).

- **Chemical Quest**
  - Explore structural similarity using numeric chemical identifiers or Simplified Molecular Input Line Entry System (SMILES) strings.

*PBPK and IVIVE tools rely upon US EPA's httk R package

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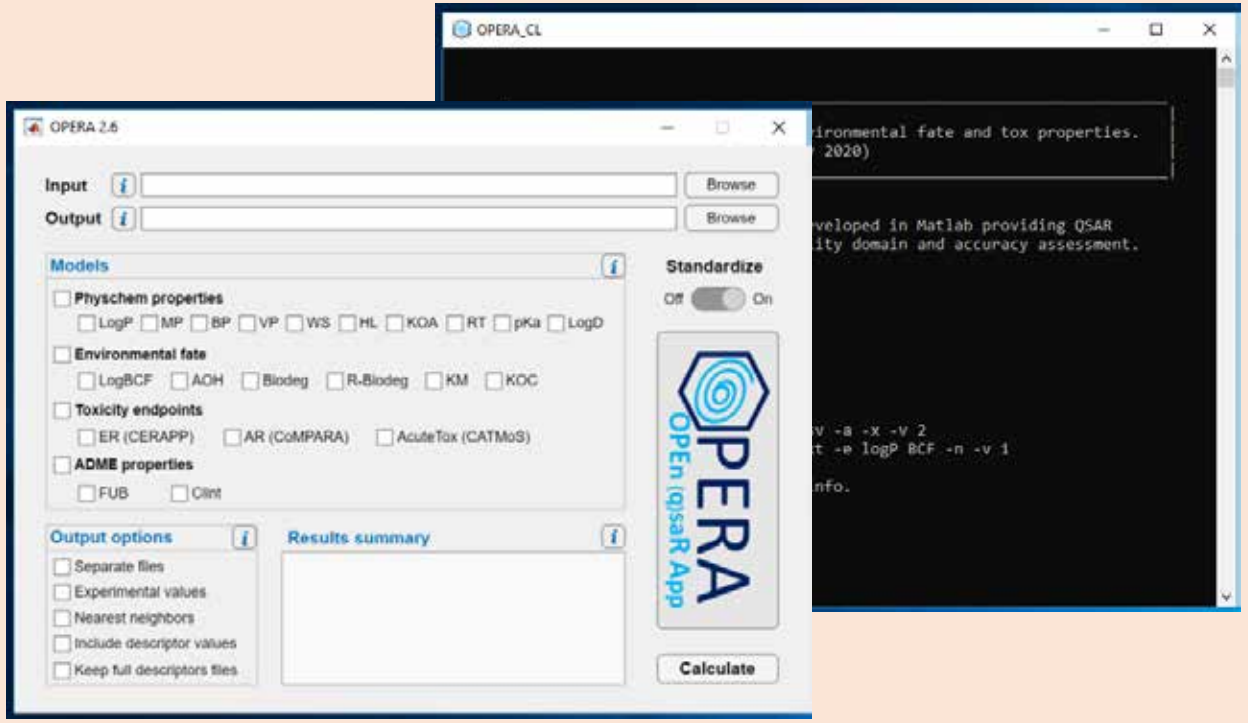
MAIN RESULTS: OPEN STRUCTURE–ACTIVITY/PROPERTY RELATIONSHIP APP (OPERA)

- Free and open-source quantitative structure-activity relationship (QSAR) tool: https://ntp.niehs.nih.gov/go/opera

- OPERA generates predictions of:
  - Physicochemical properties
    - Structural properties
    - Environmental fate parameters
  - Absorption, distribution, metabolism, and excretion (ADME) properties
    - Plasma fraction unbound (Fu)
    - Intrinsic clearance (CLint)
  - Toxicity endpoints
    - Estrogenic activity (models from CERAPP: Collaborative Estrogen Receptor Activity Prediction Project)
    - Androgenic activity (models from CoMPARA: Collaborative Modeling Project for Androgen Receptor Activity)
    - Acute oral toxicity (models from CATMoS: Collaborative Acute Toxicity Modeling Suite)
- Input options:
  - Structure IDs (CAS, DTXSID, InChIKey)
  - Structure files (SMILES, SDF, Mol)

- Single chemical and batch mode
- Multiple platforms (Windows and Linux)
- Command-line and graphical user interface (GUI) options
- Embeddable libraries (java, C, C++, Python)



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IMPACT/SIGNIFICANCE

- ICE
  - Tools and data are freely available to all.
  - ICE allows users to run pharmacokinetic predictions without purchasing proprietary software.
  - Users need no programming expertise.

https://ice.ntp.niehs.nih.gov/

- OPERA
  - Largest available inventory (>800,000 chemicals) of physiochemical and toxicity endpoint predictions.
  - Predictions are available via simple search in EPA Dashboard and in ICE.

https://ntp.niehs.nih.gov/go/opera

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