NICEATM Computational Tools and Resources Supporting Alternative Test Method Development and Evaluation

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Role of Computational Approaches in Chemical Safety Testing

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) develops and assesses alternatives to animal use for chemical safety testing. NICEATM reviews large amounts of data from a wide variety of in vivo and in vitro test methods that inform on a chemical's potential bioactivity. Computational tools and resources play a critical role in data evaluations such as:

- Aggregating and tagging data relative to toxicity endpoints of regulatory interest
- Predictive modeling of in vivo toxicities using biologically relevant in vitro assay data
- Exploring how chemical properties influence bioactivity patterns or assay predictive performance
- Relating in vitro assay activity concentrations to in vivo doses and potential human exposures
- Mapping high-content data to biological systems to provide context needed for interpretation
- Generating predicted values needed in modeling where experimental data are not available

The Integrated Chemical Environment

The Integrated Chemical Environment (ICE) is an access point for NICEATM data and tools. Organized around toxicity testing, ICE aims to make it easier for users with limited computational toxicology experience or experience with the non-animal methods to explore tools supporting the advancement of non-animal approaches.

ICE provides free online access to:

- Curated in vivo and in vitro data related to toxicity testing
- In silico toxicity and parameter predictions and chemical property data
- Curated lists of chemicals with well-characterized toxic effects (reference chemical lists)
- Computational tools for chemical characterization and predicting toxicity

ICE supports:

- Data integration: brings together available data, including data on formulations
- Results exploration: enables dynamic, graphical exploration with publication-quality graphics
- Data analysis: allows characterization of data using online workflows
- FAIR (findable, accessible, interoperable and reusable) data

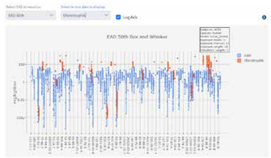
In Vitro to In Vivo Extrapolation

$C_{ss} = \frac{Dose}{CL_r + CL_h}$

The In Vitro to In Vivo Extrapolation (IVIVE) tool uses high-throughput in vitro data available from ICE to estimate an in vivo equivalent administered dose (EAD).

Choose from:

- One-compartment pharmacokinetic (1C PK) model including population simulation
- Three-compartment physiologically based pharmacokinetic (PBPK) models using the Environmental Protection Agency's (EPA) *httk* R package
- Species-specific (rat/human) predictions
- Multiple dosing routes



With the IVIVE tool users can:

- Obtain estimates of in vivo exposure levels that could cause an adverse effect
- See how EAD values differ for chemicals with similar in vitro bioactivity or chemical structure
- Gain insight on the suitability of in vitro assays for predicting the effect level for in vivo endpoints

New for 2020:

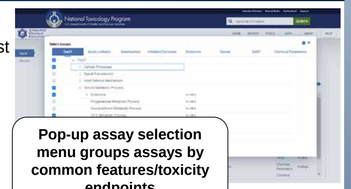
- Uploading user-supplied in vitro data for use in modeling
- Expanded models
- Improved user control of exposure scenario
- Better assay selection using ICE's assay annotations

Stand-alone version available for use with custom datasets: **https://github.com/NIEHS/ICE2.2_IVIVEpipeline**

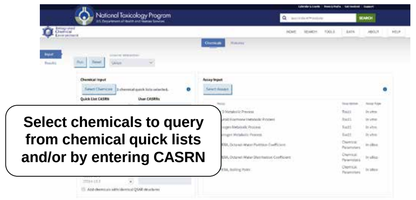
ICE Search and Data

Search ICE data by toxicity endpoint

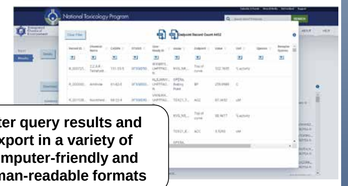
- ICE data is organized by toxicity endpoints of regulatory interest
- ICE includes OPERA predictions for >800,000 chemicals for toxicity endpoints and chemical parameters useful in modeling
- Data organization leverages expert curation and mapping to establish terminologies to support interoperability
- Chemical quick lists offer easy searching options and can be useful in test method evaluation



Pop-up assay selection menu groups assays by common features/toxicity endpoints



Select chemicals to query from chemical quick lists and/or by entering CASRN



Filter query results and export in a variety of computer-friendly and human-readable formats

Access Tox21 data

- ICE offers a curated version of Tox21 high-throughput screening data, including ToxCast data
- Tox21 curation includes curve-fit assessment and chemical QC integration
- Assays mapped to modes of action for toxicity endpoints via their mechanistic targets

Contact Us

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

To get announcements of ICE updates and other NICEATM activities, visit the NIH mailing list page for NICEATM News at https://list.nih.gov/cgi-bin/wa.exe?SUBED1=niceatm-l&A=1 and click "Subscribe."

https://github.com/NIEHS/OPERA

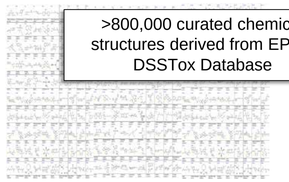
Open Structure-Activity/Property Relationship App (OPERA)

OPERA is a free and open-source quantitative structure-activity relationship (QSAR) tool. OPERA predictions include a wide range of toxicity endpoints of regulatory interest and properties that describe how a chemical interacts with its environment. These include:

- Physchem properties
  - General structural properties
  - Environmental fate
    https://jcheminf.biomedcentral.com/articles/10.1186/s13321-019-0384-1
- ADME properties
  - Plasma fraction unbound (Fu)
  - Intrinsic clearance (Clint)
- Models for Toxicity Endpoints
  - CERAPP: **C**ollaborative **E**strogen **R**eceptor **A**ctivity **P**rediction **P**roject
    https://ehp.niehs.nih.gov/15-10267/
  - CoMPARA: **C**ollaborative **M**odeling **P**roject for **A**ndrogen **R**eceptor **A**ctivity
    https://doi.org/10.1289/EHP5580
  - CATMoS: **C**ollaborative **A**cute **T**oxicity **M**odeling **S**uite
    https://doi.org/10.1016/j.comtox.2018.08.002

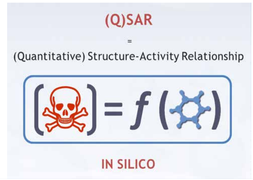
OPERA Predictions Available in ICE

Model	Description
CATMoS	Acute Oral Toxicity measures (GHS and EPA categories as well as LD50)
CERAPP	Estrogen receptor binding and agonist and antagonist activity
CoMPARA	Androgen receptor binding and agonist and antagonist activity
BP	Boiling point
Clint	Human hepatic intrinsic clearance
Fu	Human plasma fraction unbound
HL	Henry's Law constant
KOA	Octanol/air partition coefficient
LogD	Octanol-water distribution coefficient
LogP	Octanol-water partition coefficient
MP	Melting point
pKa	Acidic dissociation constant
VP	Vapor pressure
WS	Water solubility at 25º C

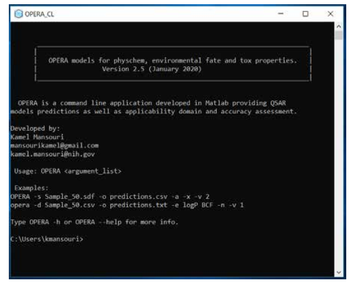


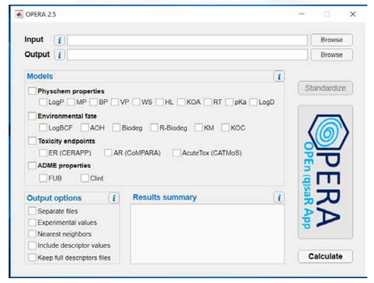
>800,000 curated chemical structures derived from EPA's DSSTox Database

Predictions



OPERA standalone app





- Free, open-source and open-data
- Single chemical and batch mode
- Multiple platforms (Windows and Linux)
- Command line and GUI options
- Embeddable libraries (java, C, C++, Python)

https://github.com/NIEHS/OPERA
https://ntp.niehs.nih.gov/go/opera
https://doi.org/10.1186/s13321-018-0263-1

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