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 evaluates alternatives to animal use for chemical safety testing. As part of these activities, 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 access and evaluations such as:

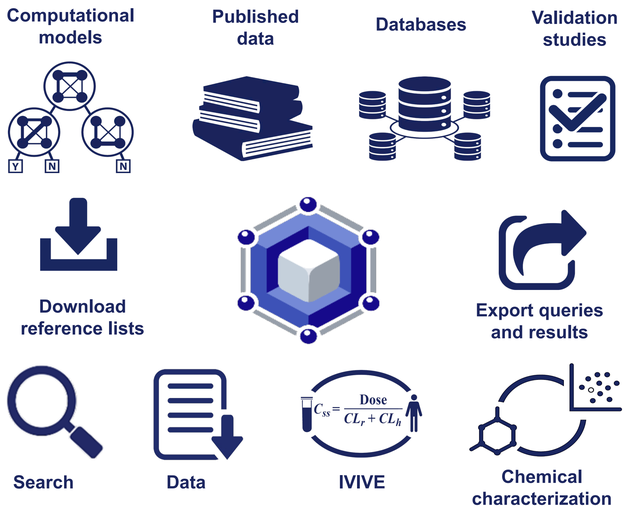
- Aggregating and tagging data relative to toxicity endpoints of regulatory interest.
- Predictive modeling of in vivo toxicities using biologically relevant in vitro assay data.
- Exploring how chemical properties influence bioactivity patterns or assay predictive performance.
- Relating in vitro assay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

The Integrated Chemical Environment (ICE)

ICE is an access point for NICEATM data and tools. ICE allows users with limited computational expertise to explore and utilize these data and tools in the development and application of new approach methodologies.

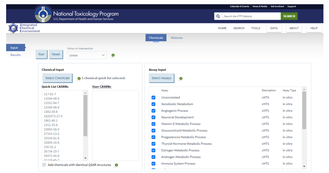
ICE provides free online access to:
- Curated in vivo and in vitro data related to toxicity testing.
- In silico toxicity and parameter predictions and chemical property data.
- Curated lists of chemicals with well-characterized toxic effects (reference chemical lists).
- Computational tools for chemical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

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



ICE Search and Data

The ICE Search tool can query assay and chemical property data for over 10,000 chemicals.
- ICE data are organized by toxicity endpoints of regulatory interest.
- ICE includes quantitative structure-activity relationship (QSAR) predictions for >800,000 chemicals for toxicity endpoints and chemical parameters useful in modeling.
- Data organization and annotation leverages expert curation and mapping to establish terminologies to support interoperability.
- Chemical quick lists offer fast and easy searching options and can be useful in test method evaluation.



In Vitro to In Vivo Extrapolation (IVIVE)

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

The In Vitro to In Vivo Extrapolation (IVIVE) tool uses high-throughput in vitro data from the Tox21 program to estimate an in vivo equivalent administered dose (EAD) that would result in the plasma concentration of a chemical equal to the activity concentration in a given in vitro assay.

Modeling options include:
- One-compartment pharmacokinetic model including simulation of population diversity.
- Three-compartment physiologically based pharmacokinetic (PBPK) models using the U.S. Environmental Protection Agency's (EPA) *httk* R package. (http://dx.doi.org/10.18637/jss.v079.i04)
- Species-specific (rat/human) predictions.
- Multiple dosing routes (intravenous, oral, inhalation).

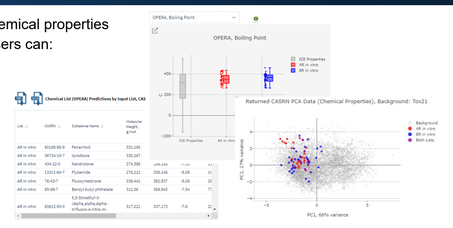
With the IVIVE tool users can:
- Obtain estimates of in vivo exposure levels that could cause an adverse effect.
- See how EAD values differ for chemicals with similar in vitro bioactivity or chemical structure.
- Gain insight on the suitability of in vitro assays for predicting the effect level for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

Stand-alone version available for use with custom datasets:
https://github.com/NIEHS/ICE_IVIVEpipeline

Chemical Characterization

The Chemical Characterization tool queries chemicals for available physiochemical properties and ADME properties predicted by the OPEn q(sar) App (OPERA) model. Users can:

- Examine properties of ICE Chemical Quick Lists or user-provided CASRNs.
- Compare the properties of two sets of chemicals.
- Results are returned as:
  - Summary table of chemical properties.
  - Interactive plots for visual comparisons of individual parameters.
  - Principal component analysis (PCA) plots.



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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

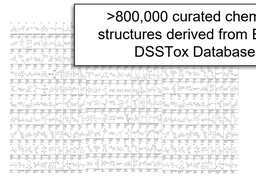
Open Structure-Activity/Property Relationship App (OPERA)

OPERA is a free and open-source 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:

- Physicochemical properties
  - General structural properties
  - Environmental fate
    https://jcheminf.biomedcentral.com/articles/10.1186/s13321-019-0384-1
- ADME properties
  - Fraction unbound to plasma proteins (Fu)
  - Intrinsic clearance (Clint)
- Models for toxicity endpoints
  - CERAPP: **C**ollaborative **E**strogen **R**eceptor **A**ctivity **P**rediction **P**roject (https://doi/10.1289/ehp.1510267)
  - 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)

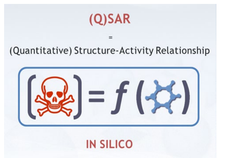
OPERA Predictions Available in ICE

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 25° C

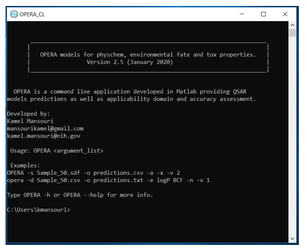


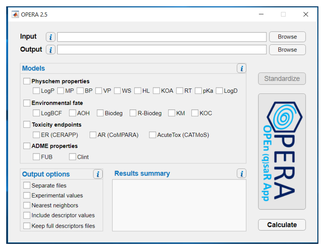
>800,000 curated chemical structures derived from EPA's DSSTox Database

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

Acknowledgements

ICE has been funded in whole or in part with federal funds from the National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN273201500010C.

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