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Integrated Chemical Environment: An Advanced Platform Aiding NAM-Based Chemical Assessments

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Integrated Chemical Environment

- The Integrated Chemical Environment (ICE) is an openly accessible resource containing curated chemical property and bioactivity data as well as tools for summarizing, analyzing, and understanding these data. ICE was developed by the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) to support development and evaluation of new approach methodologies (NAMs) that replace or reduce the use of animals in toxicology testing.
- ICE is continuously evolving to address growing data resources, support regulatory needs, and incorporate advanced features within its tools.

- **ICE provides:**
  - Curated in vivo and in vitro toxicity testing data, in silico toxicity predictions, and experimental or predicted physicochemical property data (Daniel et al. 2022).
  - Interactive computational tools that characterize, analyze, and predict bioactivity for user-defined or ICE-provided chemical lists.

ICE Data

ICE supports:
- FAIR (findable, accessible, interoperable and reusable) principles.
- Data integration: brings together disparate data types.
- Data analysis: allows characterization of data with user-friendly workflows.
- Filtering: multiple interactive filtering options provided throughout ICE.
- Tool interoperability: send selected chemicals from results across multiple ICE tools and to other resources.
- Results exploration: enables dynamic interactive visualizations yielding publication quality graphics.

ICE Tools

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

New Features in ICE v4.0

PBPK and IVIVE Tools Feature Enhancements:
- ICE PBPK (physiologically based pharmacokinetic) and IVIVE (in vitro to in vivo extrapolation) tools now incorporate a gestational model from the U.S. Environmental Protection Agency (EPA)'s httk package (v2.2.2, released February 2023; Kapraun et al. 2022).
- Users modeling inhalation exposure now have the option of selecting a dose unit of ppmv (parts per million by volume) rather than the existing option of µM (micromolar).

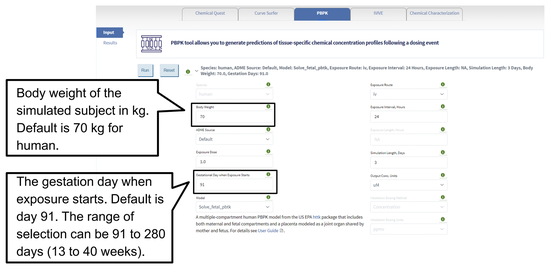
Exposure Predictions:
- ICE tools now integrate exposure predictions from the SEEM3 (Systematic Empirical Evaluation of Models) model (Ring et al. 2019).
- Exposure predictions can be accessed through a download file in the ICE Data Sets page and the ICE REST API (Application Programming Interfaces supporting the Representational State Transfer architectural style). These predicted exposure data can also be compared to the equivalent administered doses (EADs) predicted by the IVIVE tool.

Search Results Redesign:
- A completely redesigned Search results interface features new summary interactive visualizations.

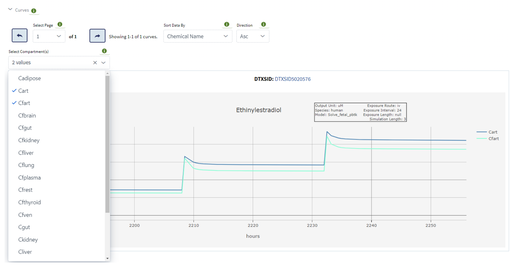
Chemical Name Input Option:
- ICE tools and the ICE REST API now accept chemical names and synonyms as input along with other pre-existing input options like CASRN, DTXSID, SMILES, and InChIKeys. This enhances comprehensive data retrieval to meet growing data needs in NAMs development.

PBPK Gestational Model

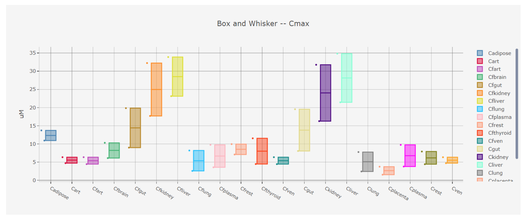
- The ICE PBPK tool can utilize either experimental or predicted parameter information to generate dynamic predictions of plasma and tissue concentration profiles following a dosing event.
- The tool now includes a gestational physiologically based toxicokinetic (PBTK) model that predicts fetal plasma concentration using the Solve_fetal_pbtk function from the EPA's httk R package version 2.2.2 (Kapraun et al. 2022, Pearce et al. 2017).
- Solve_fetal_pbtk implements a multiple-compartment human PBPK model that includes a fetal compartment. It can model chemical distribution in both maternal and fetal compartments from 91 to 280 gestation days (13 to 40 weeks).



Output provides filtering options to compare concentration-time profiles in various fetal and maternal compartments.



Boxplots facilitate comparing maximum chemical concentration (Cmax) across tissue compartments, for single or multiple chemicals. In the ICE user interface, values for each individual chemical can be seen by hovering the mouse cursor over individual data points.



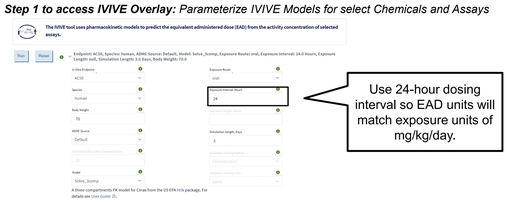
IVIVE Gestational Model

- The IVIVE tool provides the user with the daily equivalent administered dose that would result in plasma concentrations equivalent to the in vitro activity concentrations. Users can upload their own in vitro data or select assay data within ICE as input for the tool.
- This tool also features the new gestational Solve_fetal_pbtk model and requires similar input parameters as defined in the PBPK tool (Kapraun et al. 2022).
- In addition to the maternal plasma Cmax parameter EAD.50, output includes the fetal plasma Cmax EAD.50.fCmax.

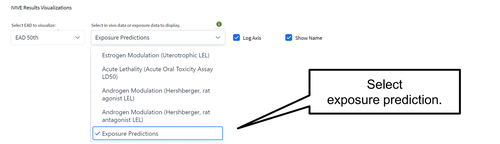
Exposure Predictions – IVIVE Overlay

- ICE v4.0 incorporates exposure predictions from EPA's SEEM3 model (Ring et al 2019). This model provides general population-level exposure predictions across multiple exposure scenarios, including consumer, dietary, far-field industrial, and pesticide sources.
- Exposure predictions for over 400,000 chemicals within the SEEM3 applicability domain are included with median, 5th, and 95th percentile estimates reported for each chemical in mg/kg/day.
- Exposure predictions have been added as an overlay option for visual comparison against the EAD estimates from the IVIVE tool.

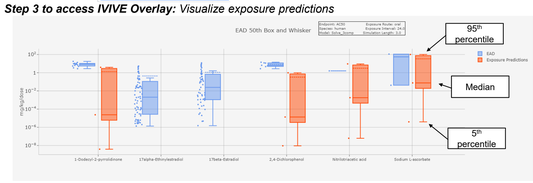
Step 1 to access IVIVE Overlay: *Parameterize IVIVE Models for select Chemicals and Assays*



Step 2 to access IVIVE Overlay: *In results page, go to "Select in vivo data to display"*

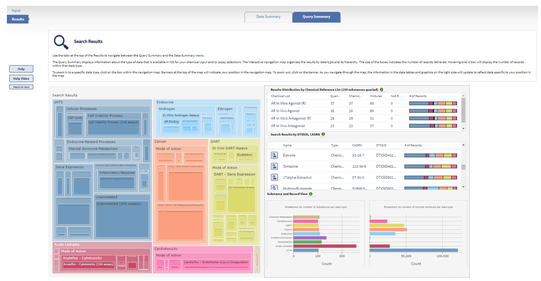


Step 3 to access IVIVE Overlay: *Visualize exposure predictions*



Search Results Redesign

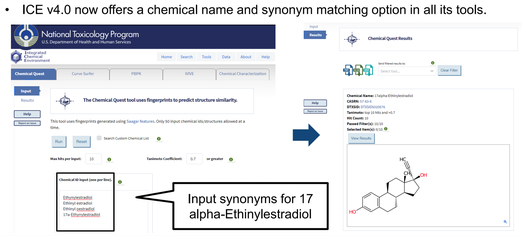
- The Search results landing page features a new interactive data navigation map that visualizes the hierarchical structure of ICE data.



- Data availability is summarized for each individual substance and each Chemical Quick List, with color bars showing the distribution of record count by data set type.
- As the user traverses the data navigation map, tables and figures are updated to reflect record counts and data set types at each hierarchical level.

Chemical Names Search

- ICE v4.0 now offers a chemical name and synonym matching option in all its tools.



Summary

- ICE tools allow users to explore and leverage ICE's ever-growing curated in silico, in vitro, and in vivo data sets for chemical analysis and NAMs-based assessments.
- ICE PBPK and IVIVE tools can provide important context to facilitate comprehensive chemical safety assessments.
  - The new gestational model included in PBPK and IVIVE tools can be used for modeling human maternal and fetal chemical distribution through 91 to 280 gestation days (13 to 40 weeks) following oral or intravenous injection route of exposure.
  - The model can predict fetal internal chemical concentration resulting from maternal exposure, which can help provide context for dosimetry for potential developmental toxicity of chemicals.
- The integration of population-level exposure predictions provides users with a more comprehensive context for chemical hazard.
  - Exposure predictions are retrievable through the API, allowing for large searches of this data set inventory comprising over 400,000 chemicals.
  - Exposure predictions can be visualized alongside IVIVE tool outputs. This allows users to compare high- and low-level percentiles to EADs, putting in vitro assays into a real-world context.
  - Annotated download files provide users with the SEEM3 predicted exposures.
- New Search results provide summary visualizations to help users contextualize and interactively explore data to identify relevant outputs optimized for the user's specific needs.

References

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More Information

Learn more about ICE at SOT 2023:

Multiple demonstrations daily at the NIEHS booth.

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

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To get announcements of ICE updates and other NICEATM activities:

Visit the NIH mailing list page for NICEATM News and subscribe:

Update: The latest release of ICE initially addressed as version 3.8 in this poster's abstract is now announced as version 4.0