National Institute of Environmental Health Sciences
Division of Translational Toxicology

ICE Tools to Facilitate PBPK Modeling and IVIVE for Various Exposure Scenarios

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Integrated Chemical Environment (ICE)

- The Integrated Chemical Environment (ICE) is an open-source resource containing curated chemical property and bioactivity data, and 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, revised, and alternative toxicity testing methods.
- ICE provides:
  - Curated in vivo and in vitro toxicity testing data and experimental or predicted physicochemical property data.
  - Interactive computational tools that characterize, analyze, and predict bioactivity for user-defined or ICE-provided lists of chemicals.
- ICE houses in vitro data from high-throughput assays for many chemicals. To provide in vivo context for these data, we can apply tools like physiologically based pharmacokinetic (PBPK) modeling and in vitro to in vivo extrapolation (IVIVE).

ICE Data

ICE Tools

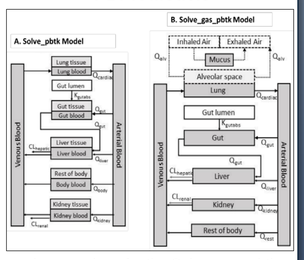
Objectives

- ICE provides user-friendly interfaces to support PBPK modeling and IVIVE under various exposure scenarios, including intravenous injection (IV), oral ingestion, and gas inhalation, based on the U.S. Environmental Protection Agency's (EPA's) httk R package.
- Case studies presented in this poster show how these ICE tools can aid in putting in vitro toxicity results into in vivo context, while taking into consideration different exposure routes.
- ICE PBPK and IVIVE tools can provide important context to facilitate comprehensive chemical safety assessments.

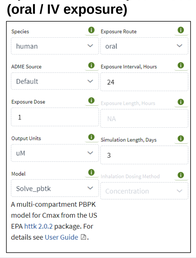
PBPK Tool Case Study

- The ICE PBPK tool utilizes both experimental and predicted parameter information to generate dynamic predictions of plasma and tissue concentration profiles following a dosing event.
- The tool provides options to select from two pharmacokinetic models from the EPA's httk R package for oral, IV, or inhalation exposure routes.
- This case study demonstrates how the tool can support identification of route-specific variability of chemical distribution across different tissue compartments.
- Input chemicals, models and simulation conditions can be selected according to user specifications.
- The unit of simulated exposure dose for the Solve_pbtk model is mg/kg/dose, while it is µM/dose (air concentration) for the Solve_gas_pbtk model. To facilitate comparison, unit conversion was done for the Solve_gas_pbtk model to make sure the same exposure level (1 mg/kg/dose) was used for simulation.

PBPK Models



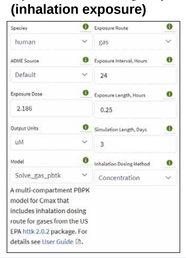
Options for Solve_pbtk Model (oral / IV exposure)



The example Solve_gas_pbtk query represents exposure dose of 2.186 µM/dose (converted from 1 mg/kg/dose) for 17-alpha-ethinyl estradiol.

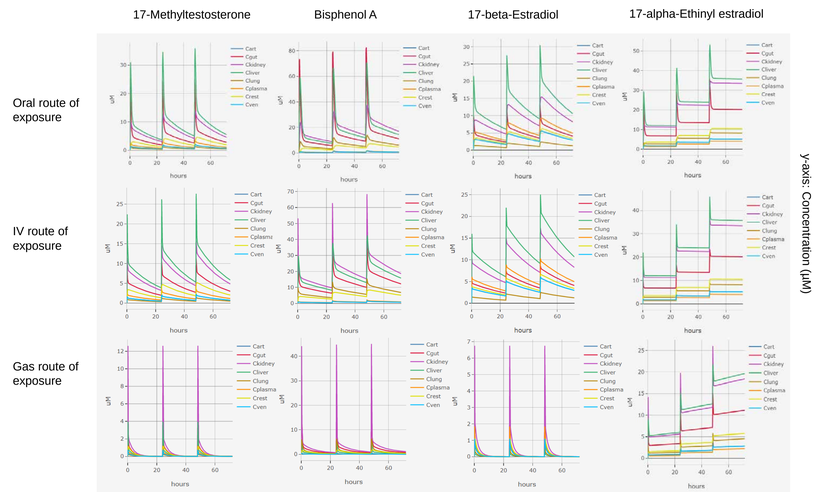
Estrogenic chemicals:
- 17-Methyltestosterone
- 17-alpha-Ethinyl estradiol
- 17-beta-Estradiol
- Bisphenol A

Options for Solve_gas_pbtk Model (inhalation exposure)



PBPK Tool Case Study

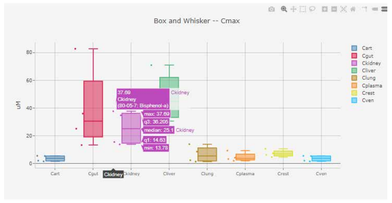
Concentration Profile Graphs Across Exposure Scenarios



- The goal of the case study is to identify route-specific variability of a group of estrogenic agonists across different tissue compartments. The chemicals were selected because of the data abundancy.
- The ICE PBPK tool provides plasma and tissue distributions for different exposure routes for the chemicals of interest.
- For the four chemicals of interest, the oral and IV routes show comparatively similar chemical clearance trends across different tissue compartments, in contrast to gas exposure route. Even though these chemicals are not volatile in nature, we used gas model for the purpose of comparison.
- Comparison of internal tissue concentration across the four chemicals indicates a higher accumulation rate for 17-alpha-ethinyl estradiol compared to others.

Distributions of Cmax for All Query Chemicals Across Tissue Compartments

Oral Route of Exposure



IV Route of Exposure

The box-and-whisker plots show distribution of Cmax values for all query chemicals across different tissue compartments. In the ICE interface, values for each individual chemical can be seen by hovering the mouse cursor over individual data points. The plots show the range, spread, and variations of Cmax values across all query chemicals, which highlight common or distinct kinetic features of these chemicals.

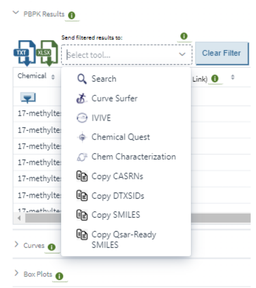
IVIVE Tool Case Study

- The IVIVE tool utilizes both experimental and predicted parameter information to translate in vitro activity concentrations to equivalent in vivo exposure estimates.
- The tool provides the option to select different in vitro assays that are annotated to mechanistic targets or modes of actions.
- It provides the user with estimated equivalent administered dose (EAD) values which results in a plasma concentration of a chemical equal to the concentration of the same chemical that exhibits an effect in an in vitro assay.
- The goal of this case study was to show how the IVIVE tool can help identify the most sensitive in vitro assay and route of exposure for a given set of chemicals based on the generated EAD values.

IVIVE Case Study

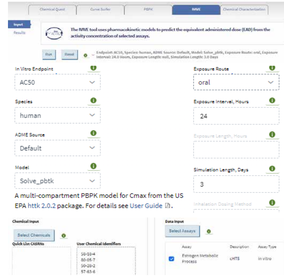
- ICE allows users either to build independent IVIVE queries or export chemicals identified as being of interest from a PBPK query (or any other ICE tool).
- Based on the comparison between internal concentration across different exposure routes from the PBPK output, we chose the same Solve_pbtk model for both oral and IV exposure routes in the IVIVE query for the same set of chemicals.

Export Chemicals from PBPK Tool



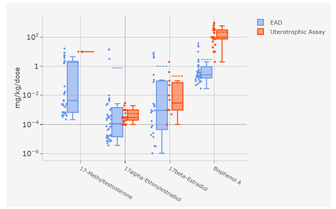
Send selected list of chemicals from PBPK output to IVIVE tool

Options for Building IVIVE Query

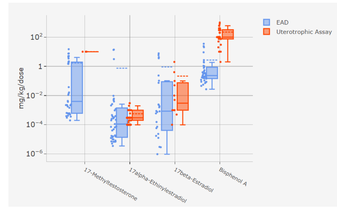


Graphical Representation of EAD Estimates

Oral Route of Exposure



IV Route of Exposure



- The box-and-whisker plots above compare EADs generated by the IVIVE tool from in vitro activity concentration (blue) with the rat uterotrophic lowest effect levels (orange) for both exposure routes.
- EAD estimates can assist in providing basic information on in vitro assay and exposure route sensitivity for the chemicals of interest.
- In this case study EADs for IV route of exposure had a slightly higher sensitivity range when compared to the oral route.

Chemical	Oral EAD Range	IV EAD Range
17-Methyltestosterone	0.000221 - 16.544	0.000199 - 14.878
17-alpha-Ethinylestradiol	3.69e-06 - 14.518	3.55e-06 - 13.966
17-beta-Estradiol	1.07e-06 - 8.526	9.71e-07 - 7.702
Bisphenol A	0.0296 - 38.505	0.027 - 35.088

Conclusion

- The ICE PBPK tool can aid in identifying the pharmacokinetic variabilities between chemicals based on different exposure scenarios.
- The PBPK tool generates time series concentration graphs representing chemical clearance rates and estimates of dynamic concentration values within each tissue compartment to illustrate differences in bioavailability in various tissues.
- The ICE IVIVE tool can predict EADs across different exposure routes, which can identify exposure levels of concern and the most conservative routes for chemical safety assessments.

References and Acknowledgments

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