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ICE PBPK Script
ICE version 3.7: 30 July 2022

ICE PBPK Intro (video one)

Welcome to the Integrated Chemical Environment, also known as ICE. In this video, we will provide a brief overview of the ICE PBPK tool. Other videos explain in detail how to set up a query using the ICE PBPK tool, and how to interpret the output of a PBPK tool query.

Physiologically based pharmacokinetic models, or PBPK models, are mathematical representations of a chemical's ADME characteristics: how the chemical is absorbed, distributed, metabolized, and excreted in the body of a human or animal. PBPK models have multiple compartments that can represent blood plasma or specific organs or organ systems. These models can be used in many applications when you need to relate an external exposure to an internal concentration.

The ICE PBPK tool allows you to generate predictions of tissue-specific chemical concentration profiles following an external exposure. The profiles are generated using PBPK models from the httk R package developed by the U.S. Environmental Protection Agency. To run the ICE PBPK tool, you need to specify dose amount, exposure route, exposure frequency, and simulation length.

The tool output provides the chemical concentration in the modeled tissue compartments over time. These outputs include Cmax, the maximum concentration of the chemical in each compartment, and Css, the concentration of the chemical at steady state.

Located throughout the tool are green information buttons to help you better understand key features and results. When you hover over a button, brief explanatory text will appear. When you click a button, more details will appear in a text box that can be moved on the screen for a clearer view.

If you encounter a problem using a tool, click the "Report an Issue" button on the left side of the display to send an email to ICE Support.

Thank you for watching our overview video on the PBPK tool in ICE. For more detailed information about the tool, go to "Help" and select "User Guides."

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How to build a query (video two)

Welcome to the Integrated Chemical Environment, also known as ICE. In this video, we will go over how to build a query in the ICE PBPK tool. This tool lets you build a physiologically based pharmacokinetic or PBPK model to explore a chemical's ADME characteristics: how the chemical is absorbed, distributed, metabolized, and excreted in the body of a human or animal.

Model Parameters

To run the PBPK tool, you need to specify the chemicals to model. You must also select a number of input parameters. We'll first look at these parameters and then talk about how to specify chemicals.

Default settings of the input parameters are provided and are shown here.

You must choose a species used for modeling. Currently, selections are limited to rat and human, with human as the default option. For certain PK parameters, if rat values are not available, human values are substituted with proper allometric scaling.

Next, we'll select the source of the ADME data used in PK modeling. Specifically, these are the hepatocyte intrinsic clearance rate and the fraction of chemical unbound in plasma. We have three options here. The Default option uses experimentally measured values wherever they are available, and in silico predictions where they are not. The second option, Measured, uses only experimentally measured values. This may result in fewer predictions because chemicals lacking these data will not be modeled. Lastly, the In Silico option uses only in silico predictions. In silico predictions used for the Default and In Silico options are provided by models in OPERA: the OPEn (Quantitative) structure–activity/property Relationship App.

The tool uses open-source PBPK models from the httk R package developed by the U.S. Environmental Protection Agency. These models generate estimates of pharmacokinetic profiles. They also predict two parameters for plasma and each tissue compartment: Cmax, the maximum concentration of the chemical in the compartment, and Css, the concentration of the chemical in the compartment at steady state.

The tool allows you to select one of two multi-compartment PBPK models for simulation. The Solve_pbtk model simulates the injection and oral gavage exposure routes, and the Solve_gas_pbtk model simulates the inhalation exposure route.

Depending on model type, you can parameterize each model for exposure route, exposure interval, exposure length, and simulation length.

For this example, we will choose the Solve_pbtk model and the oral exposure route. And keep the default parameters which are:

- Human species
- Default ADME input option
- Exposure dose of 1 mg/kg/dose

- Output unit of micromolar
- 2 hour exposure interval
- 24 hour exposure interval
- Simulation length of 3 days

Additional model information can be found in the downloadable user guide.

Chemical Input

The input field for chemicals is located below the modeling options.

You can choose an ICE Chemical Quick List by clicking on the “Select Chemicals” button. For this example, we will choose the ER In Vitro Agonist Chemical Quick List.

You can also enter chemical identifiers in the User Chemical Identifier box. You can do this by typing in one or more individual chemical identifiers. For this example, we can type in “50-28-2”, the CASRN for the chemical estradiol.

You can also paste in a list of chemical identifiers. You can use any combination of the following identifiers: CASRNs, DTXSIDs, SMILES, and InChiKeys. Examples of these identifiers are provided in the information box located in the Chemical Input field.

The PBPK tool will return results for any chemicals that have needed parameters available in ICE. While in silico parameter predictions are available for over 800,000 chemicals, we encourage users to limit input to 100 chemicals per query to improve performance and minimize wait times.

When you have built your PBPK query, click on "Run" at the top of the page. Note that the simulation may take a few minutes, depending on the model and inputs. See the results video for an overview of understanding and interpreting results.

Thank you for watching our video on how to build an PBPK query in ICE. For more detailed information on the tool, go to “Help” and select “User Guides.”

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Results (video three)

Welcome to the Integrated Chemical Environment, also known as ICE. This video will show you how to interpret results of a query run in the ICE PBPK tool. As discussed in the previous video, this tool lets you build a physiologically based pharmacokinetic or PBPK model to explore a chemical's ADME characteristics: how the chemical is absorbed, distributed, metabolized, and excreted in the body of a human or animal. We will be viewing the results of a PBPK query built in that video; if you have not yet viewed it, you may want to do so before watching this one.

Once the query is complete the window will switch to Results view.

Download results

At the top of the Results view is a heading labeled "Download PBPK Files". Click on the heading to access a link to a file in Excel format with two pages, one with query results and other with query inputs. The results page in this file provides all results described below in numerical format. Further explanation of the content of this file can be found within the information box and in the PBPK user guide.

Summary table

The first thing you'll see in the PBPK results view is an interactive table providing a summary of model results. Icons above the table allow you to download the contents in text or Excel format. Also above the table, we can see the number of rows in the table and the number of chemicals with returned results. Each row of the table represents a chemical–compartment combination. To the right, the dropdown labeled "Chemical Identifiers Not Returned By Query" has a list of any identifiers in your query that have no relevant data in ICE for PBPK modeling.

The first three columns of the table contain identifier information for each chemical. Clicking on the chemical's CASRN directs you to the test article page about that chemical in CEBS, the National Toxicology Program's Chemical Effects in Biological Systems database. This resource provides data from NTP studies that were conducted on the chemical.

Clicking on the chemical's DTXSID directs you to the U.S. Environmental Protection Agency's CompTox Chemicals Dashboard entry for that chemical. This resource provides the chemical's structure and other physicochemical and experimental properties.

The remaining table columns provide model predictions for the chemical. The fourth column provides a compartment representing a part of the body such as plasma, an organ or organ system, or "rest of the body". The fifth column provides Css, the concentration of the chemical in that compartment at steady state. The sixth column provides Cmax, the maximum concentration of the chemical in that compartment.

To filter results on a specific chemical or tissue compartment, click the filter button below the column heading and select items of interest in the dialog box that opens. The "Number of rows" listed above the table will be updated to reflect the filtered results. Clear filters by

clicking the “Clear Filter” button above the table. Any filters applied to the table will also be applied to any downloads.

Send filtered results to

Send PBPK parameters to other ICE tools to run additional queries by using the "Send filtered results to" dropdown list next to the download button. For details on the use and outputs of these tools, please refer to their respective user guides. You can also copy a list of chemical identifiers to the clipboard.

Interactive graphs showing concentrations over time

Below the table, click on the “Curves” dropdown to display interactive graphs showing the concentration profile of the chemical over time in the model compartments, also referred to as the time series. There is a separate graph for each chemical. These graphs let you inspect a chemical’s pharmacokinetic profile, which can help identify accumulation or clearance issues in a tissue compartment of interest.

You can zoom in on an area of interest in a graph by clicking and dragging around the desired focal region; double-click on the graph area to restore the original display. You can also click on the right-hand side legend to remove and add compartments from the graph. Hover the mouse over a curve to display the concentration for each compartment at the time corresponding to the position of the mouse. Hover over the graph area to display a tool bar in the top right corner that will help you interact with the graph or export it to a PNG file.

Some display options are provided above the graphs. You can filter the display for all plots to show one or more specific compartments using the “Select Compartment(s)” dropdown list. Limit the display to specific chemicals by using the “Select CASRN(s)” dropdown list.

Up to five graphs will be displayed on a page. The “Select Page” dropdown list allows you to browse through multiple pages of graphs. Use the “Sort Data By” dropdown list to sort graphs by chemical names or CASRNs; use the “Direction” dropdown list to view them in ascending or descending order.

Interactive box plots summarizing compartment data

Below the time series graphs, click on the “Box Plots” dropdown to display box plots showing the distribution of Cmax values for each modeled compartment across all chemicals in the query. This allows you to quickly scan to see if a chemical in the list clears the system rapidly relative to others.

The points in the box plot correspond to the compartment Cmax for each chemical, and the boxes show the median and interquartile range of Cmax values for each compartment across the list of tested chemicals. Hovering over each point displays the Cmax value and chemical name, as well as the summary values for the distribution of all chemicals in the query for that compartment.

As with the graphs above, hover over the plot area to display a tool bar in the top right corner that will let you zoom in and out, click on the legends to remove a compartment, and save the plot as a PNG file.

Thank you for watching our video on how to view query results for the ICE PBPK tool. For more detailed information on the tool, go to “Help” and select “User Guides.”