ICE IVIVE Video Script
ICE version 3.6: 20 March 2022

ICE IVIVE Tool

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ICE IVIVE Intro (video one)

Welcome to the Integrated Chemical Environment, also known as ICE. This video will provide an overview of the ICE in vitro to in vivo extrapolation or IVIVE tool. We have other videos that review in detail how to build a query and how to interpret results in the IVIVE tool.

Here's the IVIVE tool Input view. But before we build a query, let's take a quick look at the results produced by the tool. This will help you understand the inputs better. We'll take a more detailed look at IVIVE tool results in a second video.

The IVIVE tool uses pharmacokinetic models and reverse dosimetry to relate an in vitro bioactivity concentration to an equivalent in vivo exposure. Each chemical has unique absorption, distribution, metabolism, and excretion, or ADME, properties in the body. Pharmacokinetic models can simulate these processes to put in vitro bioactivity concentrations into a more in vivo-relevant context.

The ICE IVIVE tool uses open-source pharmacokinetic and physiologically based pharmacokinetic, or PBPK, models from the U.S. Environmental Protection Agency's httk R package to predict plasma concentrations from specified doses, species, and routes. These are used to calculate the equivalent administered dose, or EAD, needed to obtain a plasma concentration equal to the in vitro bioactivity concentrations for the same chemical. For more details on the PBPK models used in the IVIVE tool go to "Help" and select "User Guides".

The IVIVE tool shows EAD predictions and other results in a summary table and two graphs. In addition to the EAD predictions, the graphs can display relevant in vivo data to provide context to the in vitro estimates.

Now let's go back to Input view. 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 the IVIVE 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 of the ICE IVIVE tool. For more information about the IVIVE 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. This video will show you how to build a query in the ICE In Vitro to In Vivo Extrapolation or IVIVE tool.

Model Parameters

To run the IVIVE tool, you must specify both the chemicals and in vitro assay data. Before we review those inputs, though, we're going to look at the modeling options.

You will need to specify an in vitro endpoint, species, type of pharmacokinetic model, and dosing parameters. Default settings are provided and are shown here.

For the in vitro endpoint, you can choose between the default option, which is the half-maximal activity concentration, or AC50, or the activity concentration at cutoff, or ACC.

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

Next, we select the source of the absorption, distribution, metabolism, and excretion, or ADME, data used in pharmacokinetic modeling. Specifically, these are the hepatocyte intrinsic clearance rate and fraction of chemical unbound in plasma. We have three options here:

- The Default option uses available experimentally measured values, with in silico predictions used where experimental data are not available.
- The second option, Measured, only uses experimentally measured values, which may result in fewer predictions.
- Lastly, the In Silico option uses only in silico predictions as inputs. These are generated by the OPEn structure–activity/property Relationship App, or OPERA.

The IVIVE tool allows you to select one of four pharmacokinetic models for calculating an equivalent administered dose, or EAD. These include:

- A one-compartment population-based pharmacokinetic model.
- A three-compartment pharmacokinetic model.
- A multi-compartment PBPK model for oral and injection exposure routes.
- A multi-compartment PBPK model for the inhalation exposure route.

The three-compartment and multi-compartment models are from the U.S. Environmental Protection Agency's httk R package. The one-compartment model bases its EAD predictions on simulations of steady-state plasma concentration, or Css. The three-compartment and multi-compartment models base their EAD predictions on simulations of maximum plasma concentration, or Cmax.

Depending on model type, you can specify parameters for the model like exposure route, exposure interval, exposure length, and simulation length.

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

Chemical Input

The input fields for chemicals and in vitro assay data are located below the modeling options.

Select chemicals for your query in the “Chemical Input” field on the left.

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. An example of these identifiers is provided in the information box located in the Chemical Input field.

Data Input

Add in vitro data to your query by using the “Data Input” field to the right of the “Chemical Input” field. Select assays from the ICE database by clicking the “Select Assays” button. A dialog box will open, showing two tabs: “cHTS” and “Mode of Action.”

Click on the “cHTS” tab to view high-throughput assays organized into mechanistic target categories.

Click on the “Mode of Action” tab to view assays organized by mode of action.

Use the check boxes to select the assay category of interest under either tab. Assay selection is limited to the curated ToxCast and Tox21, or cHTS, data available in ICE. For this example, under the “cHTS” tab, we will choose the assay category “Endocrine-related Processes.”

When you are finished selecting assays, click on “Finished.” The assay categories you have selected will be displayed in the text box.

Custom data Input

You can also add your own in vitro and in vivo assay data to your query.

To the right of the “Data Input” field, the “Upload Custom Data” fields allow you to upload your own data. The upper custom data field allows you to upload in vivo data that can be displayed in the Results view to compare to your model predictions. The lower custom data field allows you to upload in vitro data to be used as input for the model. Note that only chemicals with parameter values available in ICE will be used for modeling.

To download a text or an Excel template file for getting your data ready for uploading, click on the green information button beside the field heading, and then click on the appropriate link to download the template file that will work best for your data.

To upload your file, you can use the “Upload” button or drag and drop your input file from a file explorer window. The in vivo data will not be displayed in Input view but can be viewed in the Results view graphs. Data from an in vitro data file will be displayed in the Chemical Input and Data Input fields in Input view, and will also be visible in the Results view outputs.

Now that you have built your IVIVE query, click on “Run” at the top of the page to run it. The query may take a few moments to run. We’ll review the query results and how to interpret them in a separate video.

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

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 in vitro to in vivo extrapolation or IVIVE tool. We will be viewing the results of an IVIVE query built in a previous video. If you have not yet viewed that video, you may want to do so before watching this one.

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

Download Results

At the top of the Results view is a heading labeled “Download IVIVE files.” Open the “Download IVIVE Files” dropdown to access a link to a downloadable output file. This is an Excel file that includes input parameters and calculated equivalent administered doses, or EADs. We’ll discuss some other options for exporting your results as we’re looking at the results displays.

Summary Table

The IVIVE Results view shows an interactive table and two interactive graphs. The “text” or “Excel” thumbnails above the table provide download options for the table data. The two graphs below the table display the EAD values and the in vitro bioactivity concentration used to calculate the EADs. The bioactivity concentration is expressed as either the half-maximal activity concentration, or AC50, or the activity concentration at cutoff, or ACC, depending on what was specified in the input.

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–assay combination. Above the table and to the right, the dropdown labeled “Chemical Identifiers Not Returned By Query” provides a list of any identifiers in your query that have no relevant data in ICE for IVIVE.

The first column of the table contains a concentration–response curve button. Click on this button to send data from that row to the ICE Curve Surfer tool. This will display the activity curves for that chemical–assay combination. Refer to the Curve Surfer User Guide for details on this tool.

The next three columns contain identifier information for each chemical.

Clicking on the chemical's CASRN directs you to the page about that chemical in the NTP Chemical Effects in Biological Systems, or CEBS, database. This resource provides access to 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.

To filter results on a specific chemical, assay, mode of action, or mechanistic target, click the filter button below the column heading. This opens a dialog box where you can select items of interest. The "Number of rows" listed above the table will be updated to reflect the filtered results. The graphs below the table will also be updated based on the filtered results, and any filters you apply will be applied to data downloads. Clear filters by clicking the "Clear Filter" button above the table.

Depending on the model parameters and the chemicals, warnings may be issued about the assay results. For example, a warning note appears when using the solve_gas_PBTK model to model a chemical whose physiochemical parameters suggest that it is nonvolatile. Warnings will appear in the "Flag" column.

Send Filter Results To

You can send your IVIVE parameters to other ICE tools to run additional queries by using the "Send filtered results to" dropdown list next to the download buttons. For details on the use and outputs of the other ICE tools, refer to their respective user guides. You can also copy chemical IDs to the clipboard.

Interactive Graphs

The graphs below the results table display two interactive plots. The upper graph shows a box-and-whisker plot of EAD results. The lower graph shows a violin plot of the in vitro bioactivity input data that the EAD prediction is based on. Any filters applied to the interactive results table will also be applied to the graphs. The plots are aligned so that the EAD plot in the upper graph is directly above the bioactivity plot for the same chemical in the lower graph. The x axis of each plot is limited to displaying 20 chemicals. Use the "Select Page" dropdown and buttons above the EAD graph to select or browse pages.

Tools above the plots allow you to select data visualization options and in vivo data overlays for the EAD results.

- If you used the one-compartment model for your query, the left-hand dropdown list allows you to select the population distribution to apply to your EAD results: either the 50th or upper 95th percentile of the steady-state plasma concentration, or Css. If you used the three-compartment or multi-compartment model, the only option is to view results based on the 50^{th} percentile of maximum plasma concentration, or Cmax. Simulation of population variability of physiological parameter values is not currently available for these models.

- The right-hand dropdown list allows you to select in vivo data to compare to your returned EAD values. Options provided by ICE include one estrogen modulation, one acute lethality, and two androgen modulation data sets. If you uploaded your own in vivo data, you can select those to overlay on the graph as well. The labels for these data will be the ones you specified in the "Dataset" column of the upload file.
- Two check boxes to the right of the dropdown lists allow you to select other plot display options. The "Log Axis" box is checked by default. Unchecking it will change the y axis on the EAD plot from log to conventional scale. Checking "Show Name" will change the x-axis labels on both plots from CASRNs to chemical names.

Hover over either plot area to display a menu of tools in the top right corner that can be used to adjust the graph display. The camera icon on the far left side of this menu will export the graph to a publication-quality image in a PNG file.

Thank you for watching our video on interpreting results of a query run in the ICE IVIVE tool. For more detailed information on the IVIVE tool, go to "Help" and select "User Guides."