ICE PBPK Tool

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Introduction

The ICE Physiologically Based Pharmacokinetics (PBPK) tool allows you to generate predictions of plasma and tissue-specific chemical time concentration profiles following a dosing event. The ICE PBPK tool runs generalized PBPK or physiologically based toxicokinetic (PBTK) models driven by a user-specified exposure route, dose amount, and dosing frequency. PBPK and PBTK models both represent absorption, distribution, metabolism, and excretion (ADME) processes, but are named differently to indicate different fields of the model to be applied.

The ICE PBPK tool output provides concentration of the chemical over time in plasma and each tissue compartment, the half-life, plasma area under curve (AUC), the maximum concentration (Cmax) in plasma and each tissue compartment, and the concentration at steady state (Css) in the plasma for some models.

The PBPK tool outputs are limited to the compartments specified in the models available in the U.S. Environmental Protection Agency's (EPA's) high-throughput toxicokinetics (httk) R package including Solve_pbtk, Solve_gas_pbtk, and Solve_fetal_pbtk (Pearce et al. 2017). Each of the httk models corresponds to a specific PBPK model type and solves for the chemical concentrations in plasma and tissue compartments defined in that PBPK model. Details on the models are available in Appendix 1.

You can run the PBPK tool interactively via the ICE graphical user interface. You can also download the workflow as an R notebook to run PBPK analyses locally.

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 resized and relocated on the screen.

The "Help" button on the left side of the display opens a text box with a brief description of the tool and links to the webpage and downloadable user guides. Below this, clicking on the "Help Video" button will provide access to videos demonstrating how to build a query and evaluate results. If you encounter a problem using a tool, click the "Report an Issue" button below the "Help" button to generate an email to ICE Support.

Building a PBPK Query

Figure 1 shows the ICE PBPK tool Input view. You can toggle between Input view and Results view by clicking tabs on the left side of the screen. The tool window defaults to Input view when it is first opened.

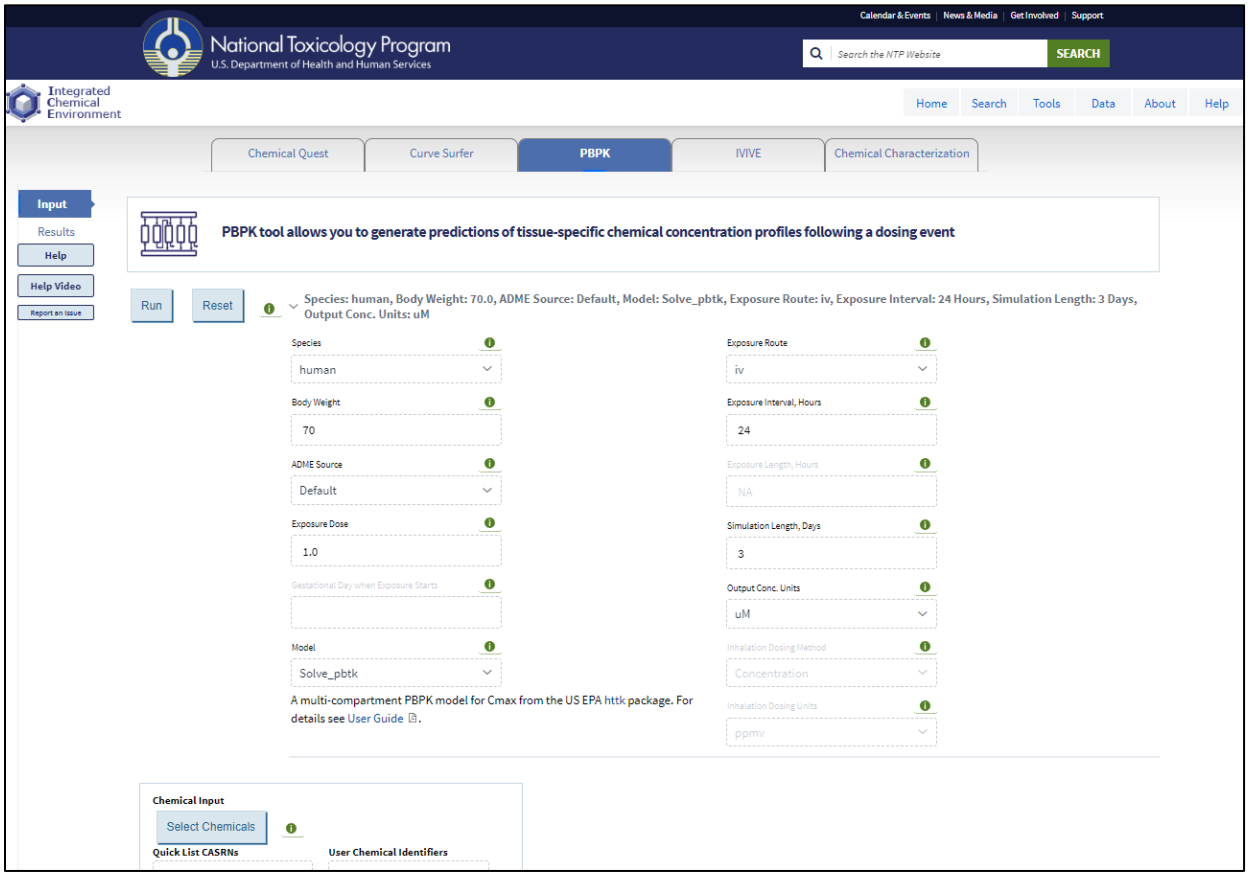

Figure 1. ICE PBPK tool Input view. [Screenshot from ICE 4.1, updated August 2024].

To run the PBPK tool, you must provide a list of chemicals as input. You must also select or input simulation conditions including species, body weight, ADME data source, exposure dose, type of pharmacokinetic (PK) model, exposure route, exposure interval, simulation length, and/or output concentration units. For the Solve_gas_pbtk model, additional input parameters such as exposure length, inhalation dosing method, and units are also required. For Solve_fetal_pbtk models, "gestational day when exposure starts" is also needed. Default parameter settings are provided.

Select Model and Parameters

Click the dropdown lists above the Chemical Input fields to select a PBPK model and additional input parameters for your query **(Figure 2)**. You can find more information on models and parameters in Appendix 1.

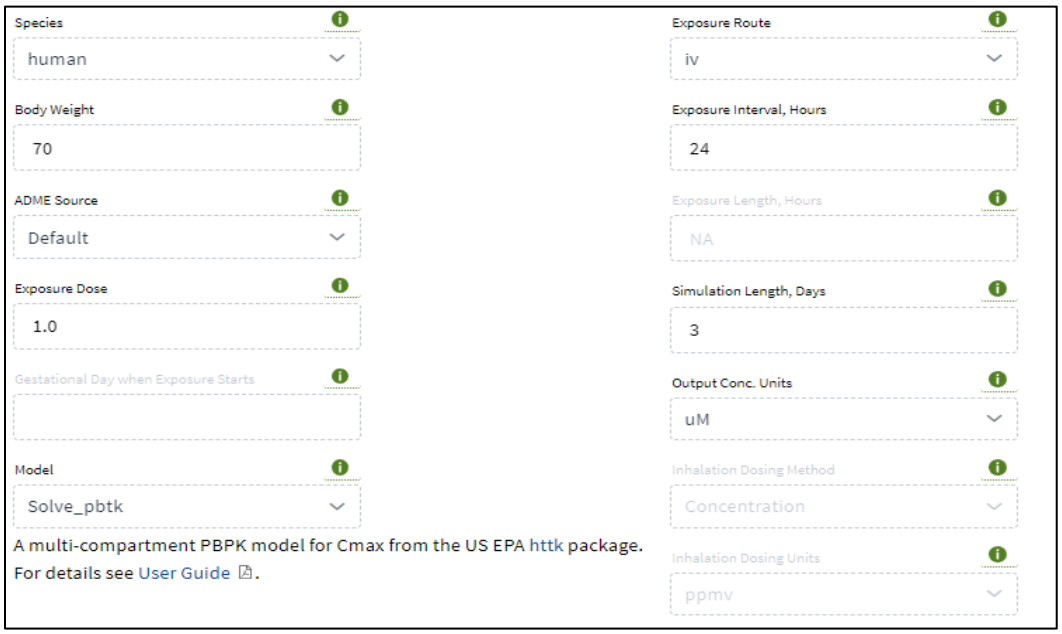

Figure 2. Click dropdown lists to specify species, exposure, model, and other model input parameters. [Screenshot from ICE 4.1, updated August 2024.]

Select Species

Select the target species that the tool will create predictions for, either human (default) or rat. For certain PK parameters, if rat values are not available, human values are substituted with proper allometric scaling. Human is the only target species available for the gestational model.

Select ADME Source

Select "Default", "Measured", or "In Silico" to specify the source of ADME parameters used to run the simulation.

- **Default:** experimentally measured values will be used when available, with in silico predictions from the Open Structure–activity/property Relationship App (OPERA) used where there is no experimental value available.
- **Measured:** only experimentally measured values will be used. This may result in fewer chemicals being modeled.
- **In Silico:** only in silico predictions from OPERA will be used.

Enter Exposure Dose

Enter the dose of a chemical to be administered. For the Solve_pbtk and Solve_fetal_pbtk models, exposure dose units are mg/kg/dose. For the Solve_gas_pbtk model, the dose describes the concentration of a chemical in air in parts per million by volume (ppmv) or µM. For both, the default value is set to 1.0.

Enter Gestation Day when Exposure Starts

This parameter is only used for the Solve_fetal_pbtk model. Enter the gestation day when exposure

starts. The range of selection is 91 to 280 days, with the default set to 91 days (13 weeks).

Select Model

Click the “Model” dropdown list at the bottom of the left column to select from three PBPK models for calculating plasma concentrations in tissues:

- **Solve_pbtk:** a multiple-compartment PBPK model from EPA’s httk R package (v 2.2.2) that includes gut, artery, vein, lung, liver, kidney, and rest-of-body compartments. The model uses the httk "Solve_pbtk" function to predict chemical distribution following exposure via the oral or intravenous injection route. This model can be run for human or rat.
- **Solve_gas_pbtk:** a multiple-compartment PBPK model from EPA’s httk R package (v 2.2.2) that includes the same compartments as the “Solve_pbtk” model but has a dosing module for modeling inhalation (gas) route of exposure. This model can be run for human or rat.
- **Solve_fetal_pbtk:** a multiple-compartment human PBPK model from EPA's httk R package (v 2.2.2) that includes maternal compartments, fetal compartments, and a placenta modeled as a joint organ shared by mother and fetus. The model simulates maternal and fetal chemical distribution for exposure via the oral or intravenous injection route starting at 91 to 280 days’ gestation. This model is for human only.

Select Exposure Route

Select the route of administration that the PBPK model will simulate. Options are specific to the model selected. They include “oral” (ingestion) or “IV” (injection) for the Solve_pbtk and Solve_fetal_pbtk models and “gas” (inhalation) for the Solve_gas_pbtk model.

Enter Exposure Interval

Enter the amount of time in hours between dosing events. The default value is 24 hours, equivalent to one dose per day. This value must be shorter than the length of the entire simulation.

Enter Exposure Length

Enter the duration in hours over which inhalation exposure is desired. This parameter is only used for the Solve_gas_pbtk model. The default value is 0.25 hours, equivalent to a 15-minute exposure.

Enter Simulation Length

Enter the exposure duration in days that the PBPK model will simulate. The parameter defaults to “3” for a three-day exposure. Dosing will occur at the frequency specified by the Exposure Interval field for the duration of the simulation.

Enter Inhalation Dosing Method

Select how the exposure is to be modeled. This parameter is only used for the Solve_gas_pbtk model. The only option currently available is “Concentration”, which models the concentration of the chemical (ppmv or µM) in air for the duration of the exposure length.

Select Inhalation Dosing Units

Select the concentration of the chemical in air as ppmv (default) or µM for the duration of the exposure length for gas exposure. This parameter is only used for the Solve_gas_pbtk model.

Select Output Concentration Units

Select the units for simulated plasma and tissue concentration as µM (default) and mg/L (currently only available for the Solve_pbtk model).

Chemical Input

In the Chemical Input field, add chemicals to your query using one or both of two input methods (**Figure 3**):

Figure 3. Input chemicals by typing chemical identifiers into the text box (right background) and/or selecting ICE Chemical Quick Lists (left background). Dialog box for selecting Chemical Quick Lists is in the foreground. [Screenshot from ICE 4.1, updated August 2024.]

Select chemicals for your query in the Chemical Input field below the model parameters on the left.

- Select one or more ICE Chemical Quick Lists by clicking the “Select Chemicals” button. This brings up a selection of ICE Chemical Quick Lists, including reference chemical lists. Select the checkboxes to choose one or more of these lists. Click “Finished” when you are done. Chemical Abstracts Service Registry Numbers (CASRNs) from chemicals in the selected list(s) will appear in the left-hand text box under Quick List CASRNs.
- Enter your own list of chemical identifiers (one per row) in the right-hand “User Chemical Identifiers” text box. You can use any combination of the following identifiers:

- CASRNs.
- Chemical names.
- Distributed Structure-Searchable Toxicity Substance Identifiers (DTXSIDs).
- Simplified molecular-input line-entry system (SMILES) strings.
- Hashed International Chemicals Identifiers (InChiKeys).

The PBPK tool will return results for over 800,000 chemicals for which the appropriate PK parameters are available in ICE. Limit input to 100 chemicals per query to facilitate working interactively.

Run PBPK Tool

Once you have selected chemicals, dosing schedule, and other parameters, click on "Run" at the top of the page to run your query. The query may take a few minutes, depending on the model and inputs. To clear all inputs, select "Reset."

Viewing PBPK Results

The window will switch to Results view after modeling is complete (**Figure 4**). Click “Input” in the top left to return to Input view to review or change your query parameters and rerun your simulation.

At the top of the Results view is a heading labeled "Download PBPK Files". Open the "Download PBPK Files" dropdown to access a link to a downloadable output file. This is an Excel workbook with two pages.

- The first page, “PBPKresults”, lists each input chemical and its predicted half-life, plasma AUC, plasma Css (for the Solve_pbtk model only), and plasma and tissue Cmax values. The columns to the right of the column headed “compartment” provide the plasma and tissue concentration–time profiles predicted from the model.
- The second page, “PBPKparameters”, lists each input chemical and the source and values of parameters used for modeling.

Interactive PBPK Results

Below the download file link, your query results appear in an interactive table (**Figure 4**). Icons above the table provide options to export your results to either a text file or an Excel file. The dropdown list next to the export icons provide other export options described below under "Send filtered results”.

To the right of the download icons and dropdown list, the number of rows and chemicals in the table are listed. There may also be a clickable heading labeled "Chemical Identifiers Not Returned By Query". This provides a list of any chemicals in your query with no relevant data in ICE for the PBPK tool. A link below the list allows you to download the list as a text file.

Use the scroll bar to the right of the table to view the entire table. The first three columns of the table contain identifier information for each chemical.

- Click on a chemical's CASRN to be directed to the available test article page about that chemical in the NTP Chemical Effects in Biological Systems (CEBS) database.
- Click on a chemical's DTXSID to be directed to the EPA CompTox Chemicals Dashboard entry for that chemical which provides the chemical structure and other physicochemical and experimental properties.

To filter results on a specific chemical or compartment, click the filter icon below the column heading and select items of interest in the dialog box that opens. The “Number of rows” and “Number of chemicals” listed above the table will be updated to reflect the filtered results, and the icon for the applied filter will turn red. Clear filters by clicking the “Clear Filter” button above the table.

Figure 4. ICE PBPK tool Results view. [Screenshot from ICE 4.1, updated August 2024.]

Interactive Curves

Concentration Profile Curves

Click on the “Interactive Curves” heading (**Figure 4**, below the table) to display the concentration profile (time series) graph for each chemical (**Figure 5**).

A separate plot is shown for each chemical returned in the results, with a line representing each compartment. The display can be filtered 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 menu.

Up to five plots will be displayed on a page. The "Select Page" feature allows you to view specific pages or use the right and left arrows to browse through plots displayed on multiple pages. Use the "Sort Data By" dropdown list to sort plots by chemical names or CASRNs; use the "Direction" dropdown list to view

them in ascending or descending order.

You can zoom in on an area of interest in a curve by clicking and dragging around the desired focal region; double-click on the plot to restore the original display. Hovering over the plots will display the concentration for each compartment at the time corresponding to the position of the cursor. Hovering over the plot area will also display a menu of tools in the top right corner that can be used to adjust the graph display. For more information about interactive graph visualization options, consult the Interactive Graphs User Guide.

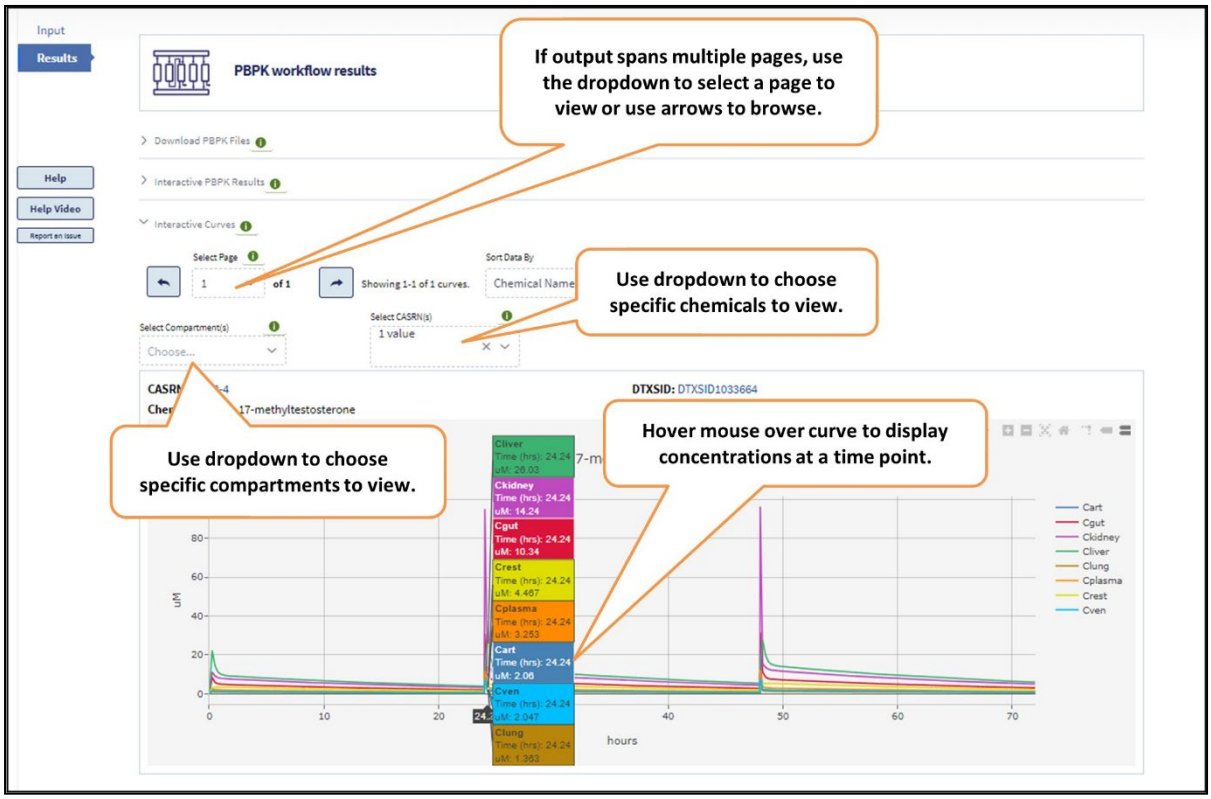

Figure 5. Curve output from ICE PBPK tool. [Screenshot from ICE 4.1, updated August 2024.]

Box Plots of Cmax Values

Click on the "Box Plots" heading (**Figure 4**, bottom of figure) to display box plots showing the distribution of Cmax values for each compartment across the chemicals in the query (**Figure 6**). The points in the box plot correspond to the compartment Cmax for each chemical, and the boxes show the median Cmax and interquartile range for each compartment. Hovering over each point displays the exact Cmax value and chemical name, as well as the summary values for the distribution of all chemicals in the query for that compartment.

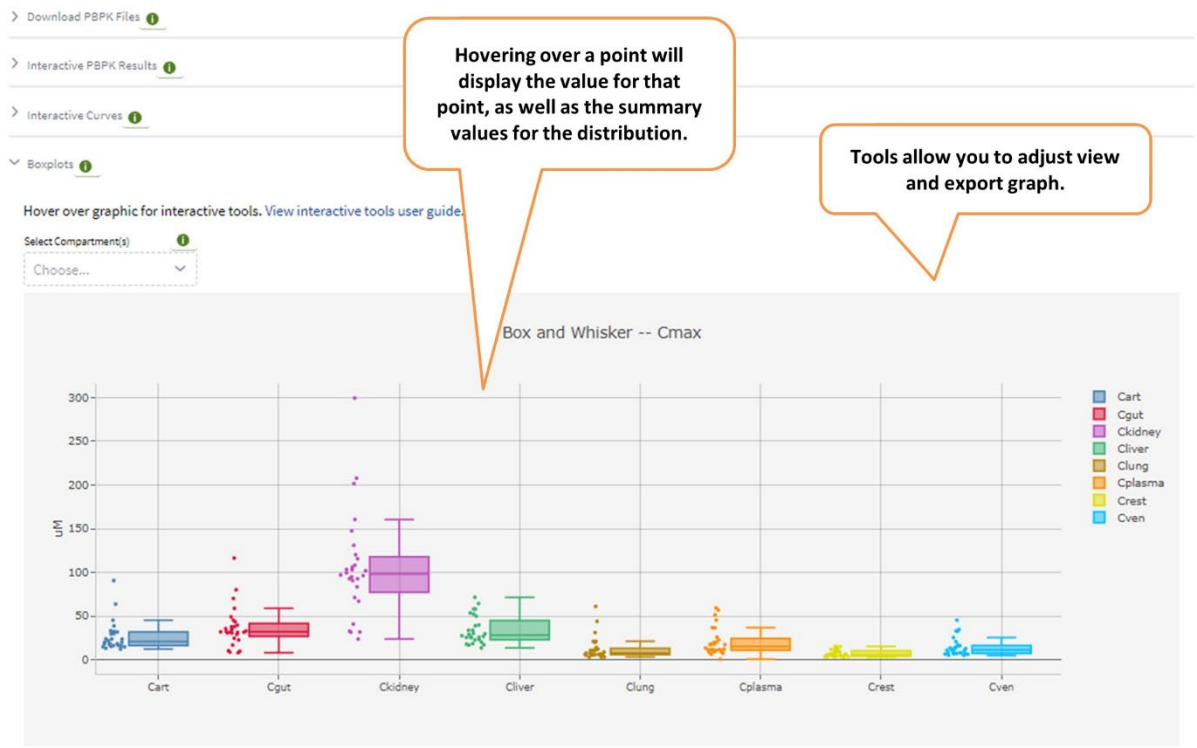

Figure 6. Box plot of compartment Cmax values for PBPK tool results. [Screenshot from ICE 4.1, updated August 2024.]

Using Results to Query Other ICE Tools

In the “Interactive PBPK Results” table, use the “Send filtered results to” dropdown list **(Figure 7)** next to the download icons to send result parameters to other ICE tools. For details on the use and outputs of these tools, refer to their User Guides.

- Click "Search" to query and retrieve all data in ICE for the selected chemicals.
- Click “Chemical Quest” to query ICE for chemicals that are structurally similar to your chemicals.
- Click “Curve Surfer” to display activity curves for chemicals that have curated high-throughput screening (cHTS) assay data in ICE.
- Click "IVIVE" to send chemicals to the In Vitro to In Vivo Extrapolation (IVIVE) tool. This tool estimates the daily equivalent administered dose that would result in the plasma concentration of a chemical equal to the activity concentration in a given in vitro assay.
- Click "Chem Characterization" to view physicochemical and ADME properties and consumer use categories for these chemicals.

You can also copy the chemical names, CASRNs, DTXSIDs, SMILES strings, or quantitative structure–activity relationship (QSAR)-ready SMILES strings to the clipboard.

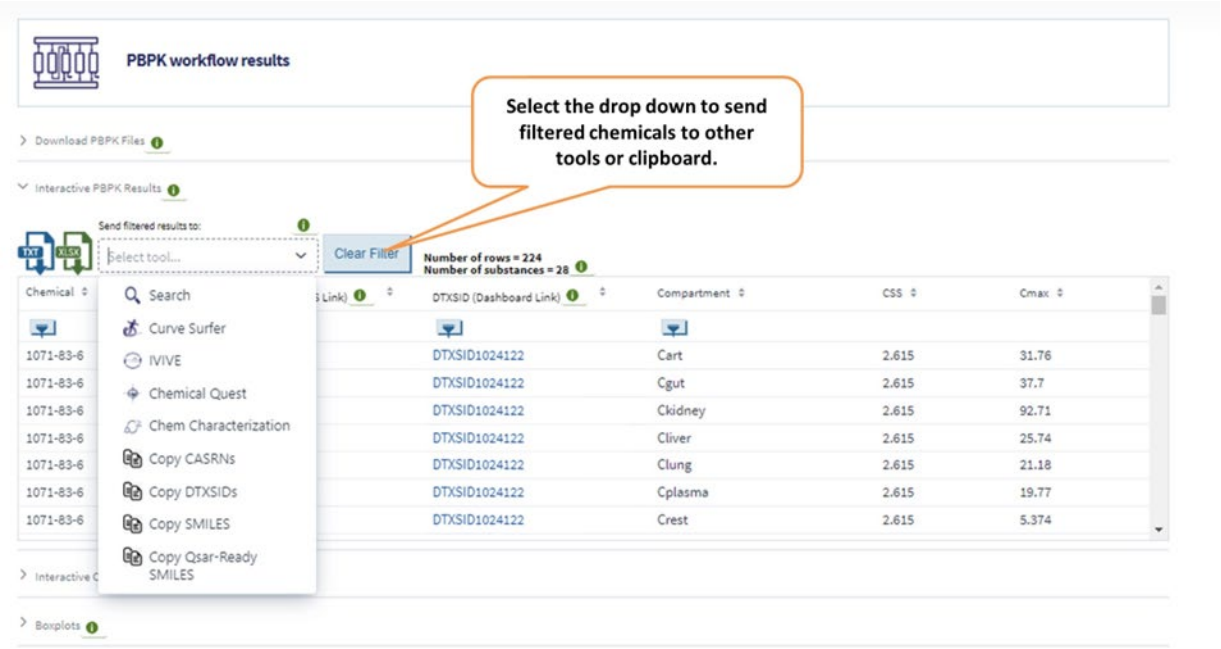

Figure 7. Send filtered results to other ICE tools. [Screenshot from ICE 4.1, updated August 2024.]

Appendix 1: How PBPK Predictions are Made

Chemical-Specific PK Parameters

To predict tissue chemical concentration profiles, the PBPK tool requires chemical-specific PK parameters. Parameters required for the ICE PBPK tool include:

- Fraction of chemical unbound to plasma protein (fu)
- Intrinsic clearance from liver (CLintrinsic)
- Renal clearance (CLrenal)
- Molecular weight (MW)
- Octanol-water partition coefficient (logP)
- Henry's Law constant (a measure of solubility of gas in a liquid)
- Acid-dissociation constant (pKa)
- Tissue:plasma partition coefficients for tissues included in a model, e.g., liver, kidney, lung, and rest of body.

ICE currently provides predicted values for most of these parameters for over 800,000 chemicals through OPERA (Mansouri et al., 2018). OPERA is a free and open-source/open-data suite of quantitative structure–activity relationship models providing predictions on fu, CLintrinsic, and physicochemical properties (i.e., logP, Henry's Law constant, pKa). The tissue:plasma partition coefficients are calculated using the Predict_partitioning_schmitt function in the httk R package (Schmitt et al. 2008; Pearce et al. 2017).

PK Models Used in the ICE PBPK Tool

The ICE PBPK tool uses PK models from the httk R package (Pearce et al. 2017) to estimate chemical concentration in compartments at the dose provided by the user. There are three PK models included in the PBPK tool (**Figure 8**).

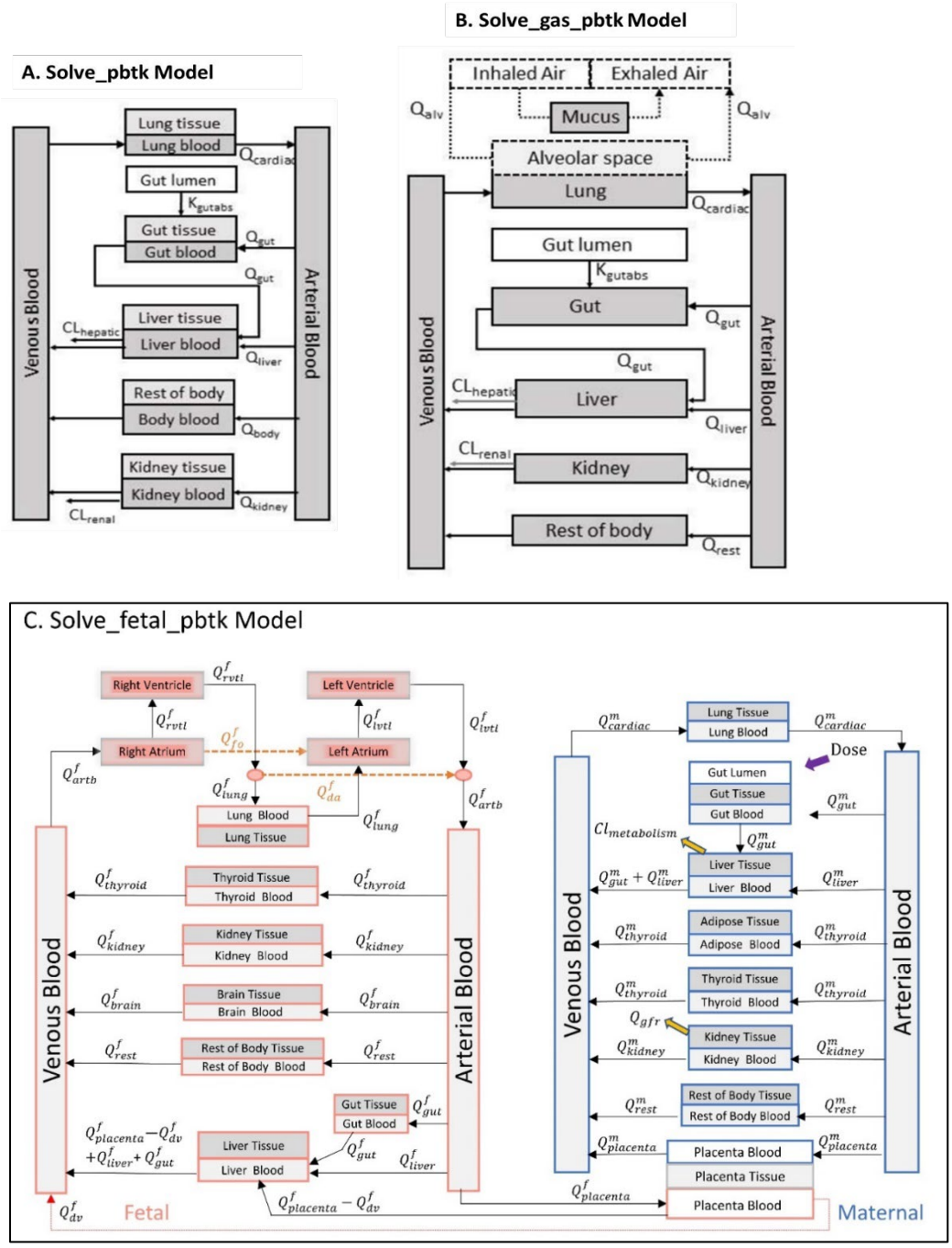

Figure 8. Structure of the PK models used in the PBPK tool. Abbreviations beginning with Q indicate blood flow, while abbreviations beginning with "CL" indicate clearance. For the Solve_fetal_pbtk model, abbreviations beginning with Q^m indicate blood flow in maternal tissues, and abbreviations beginning with Q^f indicate blood flow in fetal tissues. GFR, glomerular filtration rate; K_{gutabs}, rate constant of gut absorption (h^{-1}).

Solve_pbtk Model

Solve_pbtk (**Figure 8A**) uses the Solve_pbtk function from the httk R package (httk v 2.2.2) (Pearce et al. 2017). The function uses a multiple-compartment PBPK model to solve for compartment concentrations as functions of time after IV and oral dosing. The model can be run for human or rat. The model includes gut, artery, vein, lung, liver, kidney, and rest- of-body compartments. Each tissue compartment is regarded as perfusion rate-limited. The rate of change of the amount of chemical in each tissue compartment is described by mass balance differential equations. The elimination of chemicals is assumed to be by hepatic metabolism and passive glomerular filtration. In addition to calculating compartment concentration–time series, the ICE PBPK tool uses the Solve_pbtk function to estimate Cmax of each compartment following the specified dose.

Solve_gas_pbtk Model

Solve_gas_pbtk (**Figure 8B**) uses the Solve_gas_pbtk function from the httk R package (httk v 2.2.2) (Pearce et al. 2017, Linakis et al. 2020). The function uses an inhalation route-specific PBPK model to solve for compartment concentrations as a function of time after an inhalation exposure. The model can be run for human or rat. The model contains the same compartments as the"Solve_pbtk" model but has an additional dosing module for the inhalation (gas) route of exposure. Each tissue compartment is regarded as perfusion rate-limited. The rate of change of the amount of chemical in each tissue compartment is described by mass balance differential equations. The elimination of chemicals is assumed to be by hepatic metabolism and passive glomerular filtration. The model can currently be dosed using the chemical concentration in air, which describes exposure of an organism to a specific concentration of a chemical over the exposure length.

Solve_fetal_pbtk Model

Solve_fetal_pbtk (**Figure 8C**) uses the Solve_fetal_pbtk function from the httk R package (httk v 2.2.2) (Pearce et al. 2017, Kapraun et al. 2022). The function uses a PBPK model specified for modeling chemical distribution for human gestation days 91 to 280 following an oral or intravenous injection exposure. The function solves for maternal and fetal compartment concentrations as a function of time. The model includes both maternal and fetal compartments as well as a placenta compartment modeled as a joint organ shared by mother and fetus. The maternal compartments include gut, artery, vein, lung, liver, adipose, thyroid, kidney, placenta, and rest of body. The fetal compartments include gut, artery, vein, right ventricle, left ventricle, right atrium, left atrium, lung, liver, brain, thyroid, kidney, and rest of body. As for the other two models, each tissue compartment is regarded as perfusion rate-limited, and the rate of change of the amount of chemical in each tissue compartment is described by mass balance differential equations. The elimination of chemicals is assumed to be by hepatic metabolism and passive glomerular filtration.

Appendix 2: References and Other Resources

References Cited in this Document

Linakis MW, Sayre RR, Pearce RG, Sfeir MA, Sipes NS, Pangburn HA, et al. 2020. Development and evaluation of a high throughput inhalation model for organic chemicals. J Expo Sci Environ Epidemiol 30(5):866-877. doi: 10.1038/s41370-020-0238-y.

Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, et al. 2022. Evaluation of a rapid, generic human gestational dose model. Reprod Toxicol 113:172-188. doi: 10.1016/j.reprotox.2022.09.004.

Mansouri K, Grulke CM, Judson RS, Williams AJ. 2018. OPERA models for predicting physicochemical properties and environmental fate endpoints. J Cheminformatics 10:10. doi: 10.1186/s13321-018-0263-1.

Pearce R, Strope C, Setzer W, Sipes N, Wambaugh J. 2017. httk: R Package for high-throughput toxicokinetics. J Stat Softw 79. doi: 10.18637/jss.v079.i04.

Schmitt W. 2008. General approach for the calculation of tissue to plasma partition coefficients. Toxicol In Vitro 22:457–467. doi: 10.1016/j.tiv.2007.09.010.

For More Information

https://cran.r-project.org/web/packages/httk/index.html: Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") as in Pearce et al. (2017).

https://github.com/NIEHS: R Notebook for the downloadable IVIVE standalone application.

https://ice.ntp.niehs.nih.gov/DATASETDESCRIPTION: descriptions of data sets included in ICE, including the Tox21 data set.

Appendix 3: Abbreviations

This list includes both abbreviations used within this User Guide and abbreviations used in the ICE PBPK tool interface.

ADME: absorption, distribution, metabolism, and excretion

AUC: area under the curve

Cart: concentration in arterial compartment

CASRN: Chemical Abstracts Service Registry Number

CEBS: National Toxicology Program Chemical Effects in Biological Systems database

Cgut: concentration in gut compartment

Ckidney: concentration in kidney compartment

CLhepatic: clearance rate from liver (**Figure 8**)

cHTS: curated high-throughput screening

CLintrinsic: intrinsic clearance from liver

Cliver: concentration in liver compartment

CLrenal: clearance rate from kidney (**Figure 8**)

Clung: concentration in lung compartment

Cmax: maximum plasma concentration

Cplasma: concentration in plasma

Crest: concentration in “rest-of-body” compartment

Css: steady-state plasma concentration

Cven: concentration in venous compartment

DTXSID: Distributed Structure-Searchable Toxicity (DSSTox) Substance Identifier (U.S. Environmental Protection Agency)

EPA: U.S. Environmental Protection Agency

fu: fraction of chemical unbound to plasma protein

GFR: glomerular filtration rate

httk: high-throughput toxicokinetics

InChiKeys: hashed International Chemicals Identifiers

IV: intravenous

logP: octanol-water partition coefficient

MW: molecular weight

NA: not applicable

OPERA: Open structure–activity/property Relationship App

PBPK: physiologically based pharmacokinetic

PBTK: physiologically based toxicokinetic

PK: pharmacokinetic

pKa: acid-dissociation constant

ppmv: parts per million by volume

Q^{f}_{i}: blood flow to fetal tissue i (**Figure 8C**)

Q_i: blood flow to tissue i (**Figure 8**)

Qliver: liver blood flow rate (**Figure 8**)

Q^m_i: blood flow to maternal tissue i (**Figure 8C**)

QSAR: quantitative structure–activity relationship

SMILES: simplified molecular-input line-entry system