Facilitating NAM-Based Chemical Assessments with the Integrated Chemical Environment

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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.
- Organized around toxicity testing, ICE aims to make it easier for users with limited computational toxicology experience or experience with the non-animal methods to explore tools supporting the advancement of NAMs.

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 curated lists of chemicals with well-characterized toxic effects.

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.

Search   Chemical Quest   Curve Surfer
Chemical Characterization   IVIVE   PBPK

https://ice.ntp.niehs.nih.gov/
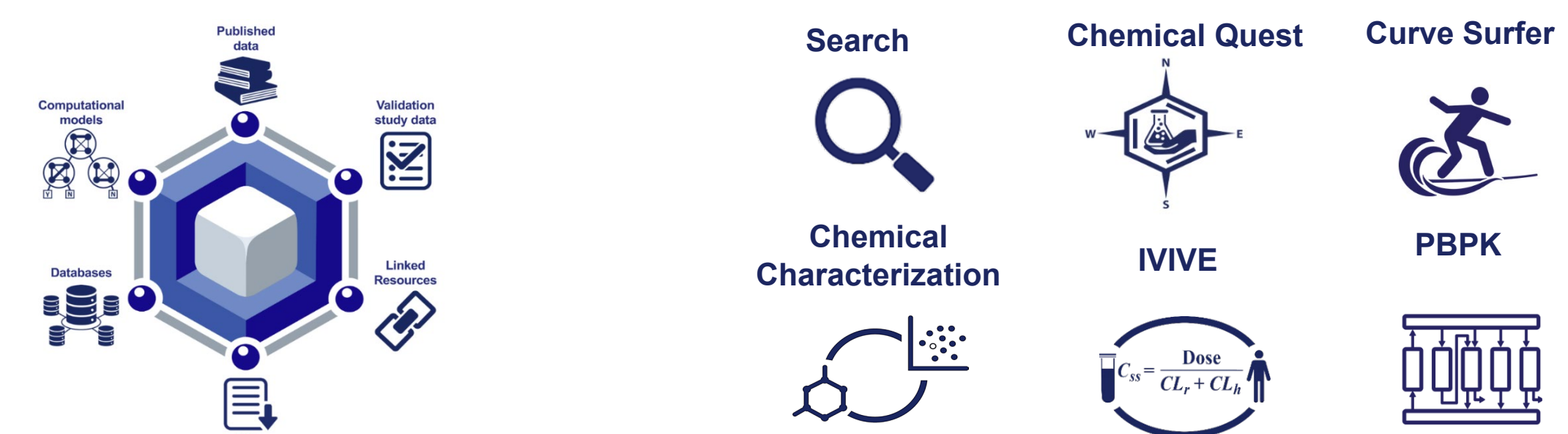
Major ICE Updates (v4.0 and v4.0.1, 2023)

Chemical Characterization Tool Updates:
- ICE Chemical Characterization tool now features reported and predicted functional use categories from the U.S. Environmental Protection Agency's (EPA's) Chemical and Products Database (CPDat), **https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat).**

Exposure Predictions:
- ICE tools now integrate exposure predictions from the EPA's SEEM3 (Systematic Empirical Evaluation of Models) model (Ring et al. 2019).
- Exposure predictions can be:
  - Accessed through the ICE Search tool.
  - Exported via the ICE REST API (Application Programming Interfaces supporting the Representational State Transfer architectural style) and as a download file in the ICE Data Sets page.
  - Compared to the equivalent administered doses (EADs) predicted by the ICE In Vitro to In Vivo Extrapolation (IVIVE) tool.
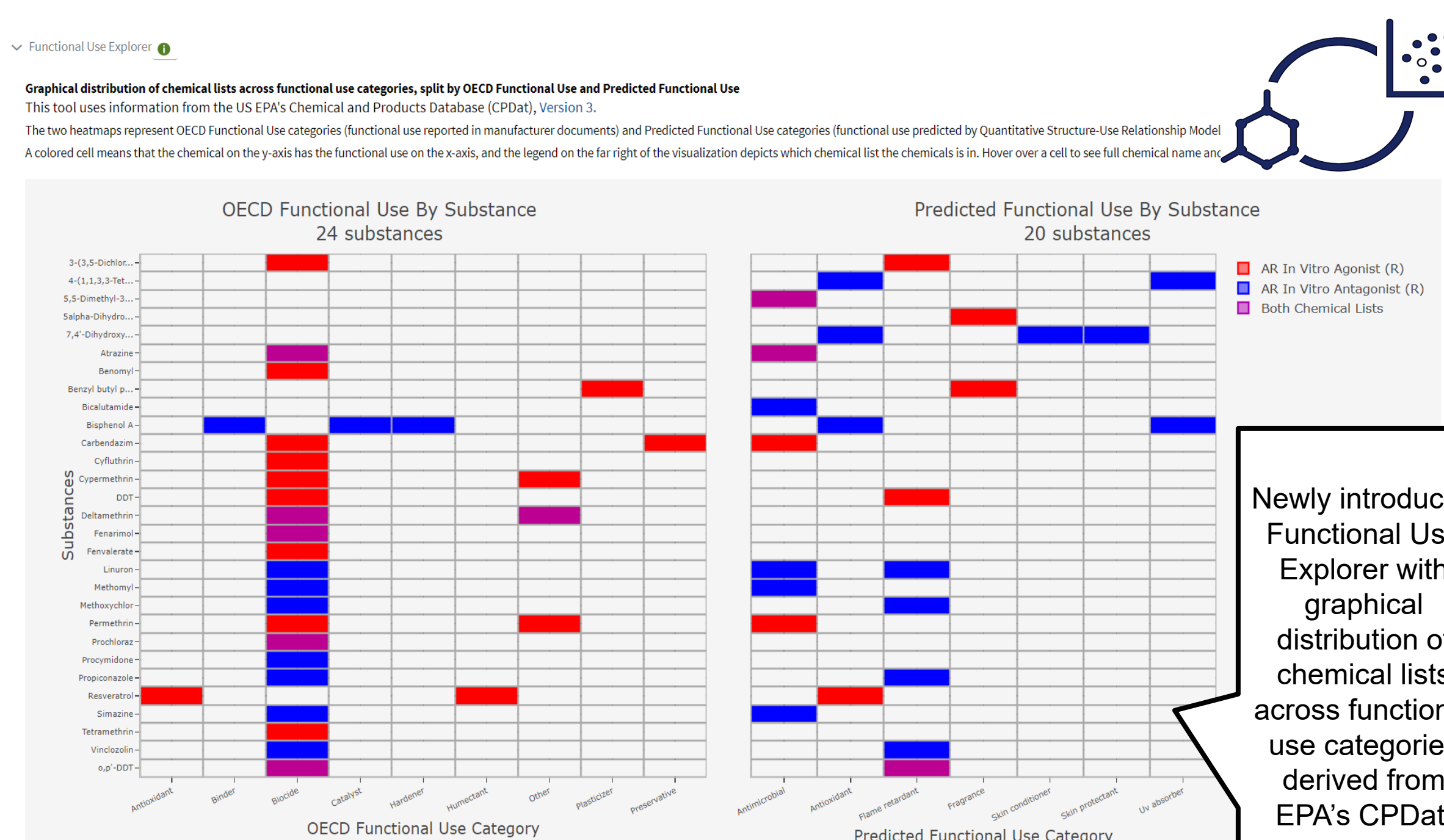
PBPK and IVIVE Tools Feature Enhancements:
- ICE Physiologically Based Pharmacokinetic (PBPK) and IVIVE tools now incorporate a gestational model from the EPA's high-throughput toxicokinetics (httk) package (v2.2.2, released February 2023; Kapraun et al. 2022, Pearce et al. 2017).
- Users modeling inhalation exposure now have the option of selecting a dose unit of ppmv (parts per million by volume) in addition to the existing option of μM (micromolar).

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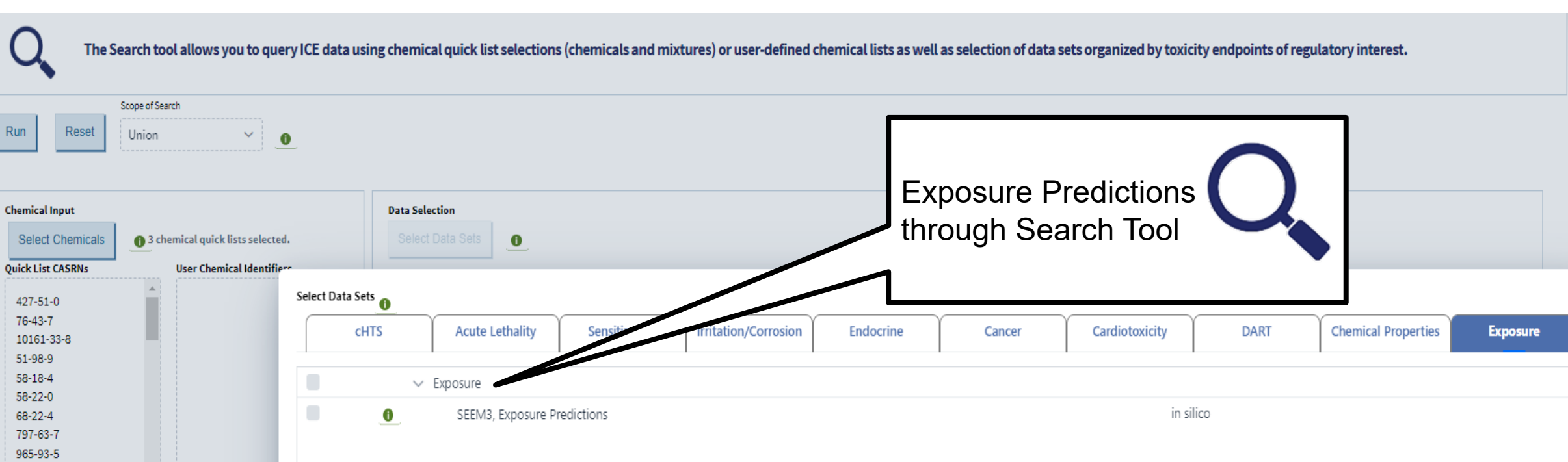- A completely redesigned Search results interface features new summary interactive visualizations.

Chemical Characterization Tool Updates

Graphical distribution of chemical lists across functional use categories, got by OECD Functional Use and Predicted Functional Use

This tool uses information from the US EPA's Chemical and Products Database (CPDat), Version 1.

The text features represent OECD Functional Use Categories reported and Predicted Functional Use categories (functional use predicted by Quantitative Structure-Use Relationship Model.

A colored cell means that the chemical on the y-axis has the functional use on the x-axis, and the legend on the right of the visualization depicts which chemical list the chemicals is in. Hover over a cell to see full chemical name.

Newly introduced Functional Use Explorer with graphical distribution of chemical lists across functional use categories derived from EPA's CPDat.

Additional information on the Functional Use Explorer is posted on Hull et al. ASCCT 2023 poster on "Curating Chemical Use Categories and Exposure Predictions to Inform Chemical Assessment".
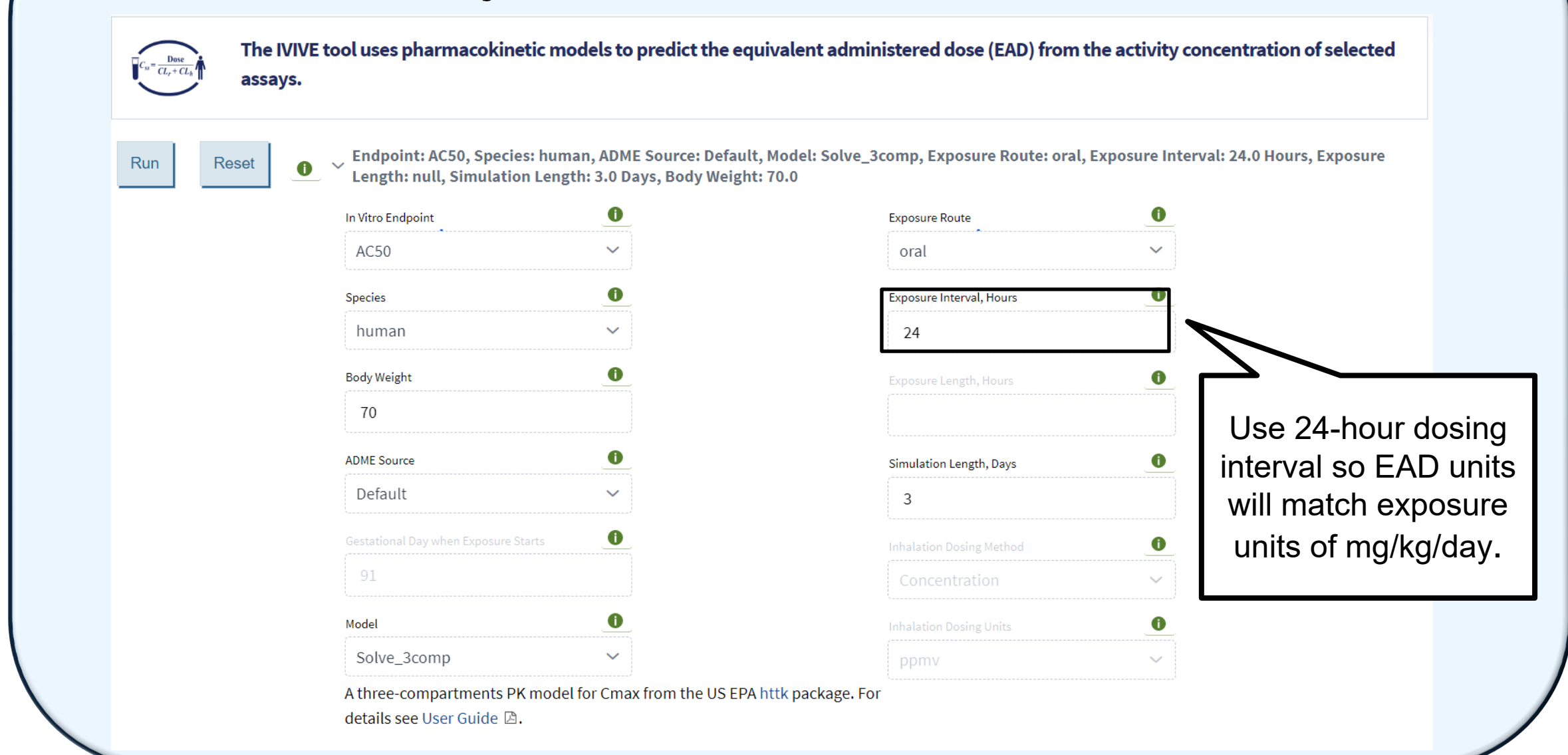
Exposure Predictions

- ICE v4.0 incorporates exposure predictions from EPA's SEEM3 model. 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 exposure estimates reported for each chemical in mg/kg/day.
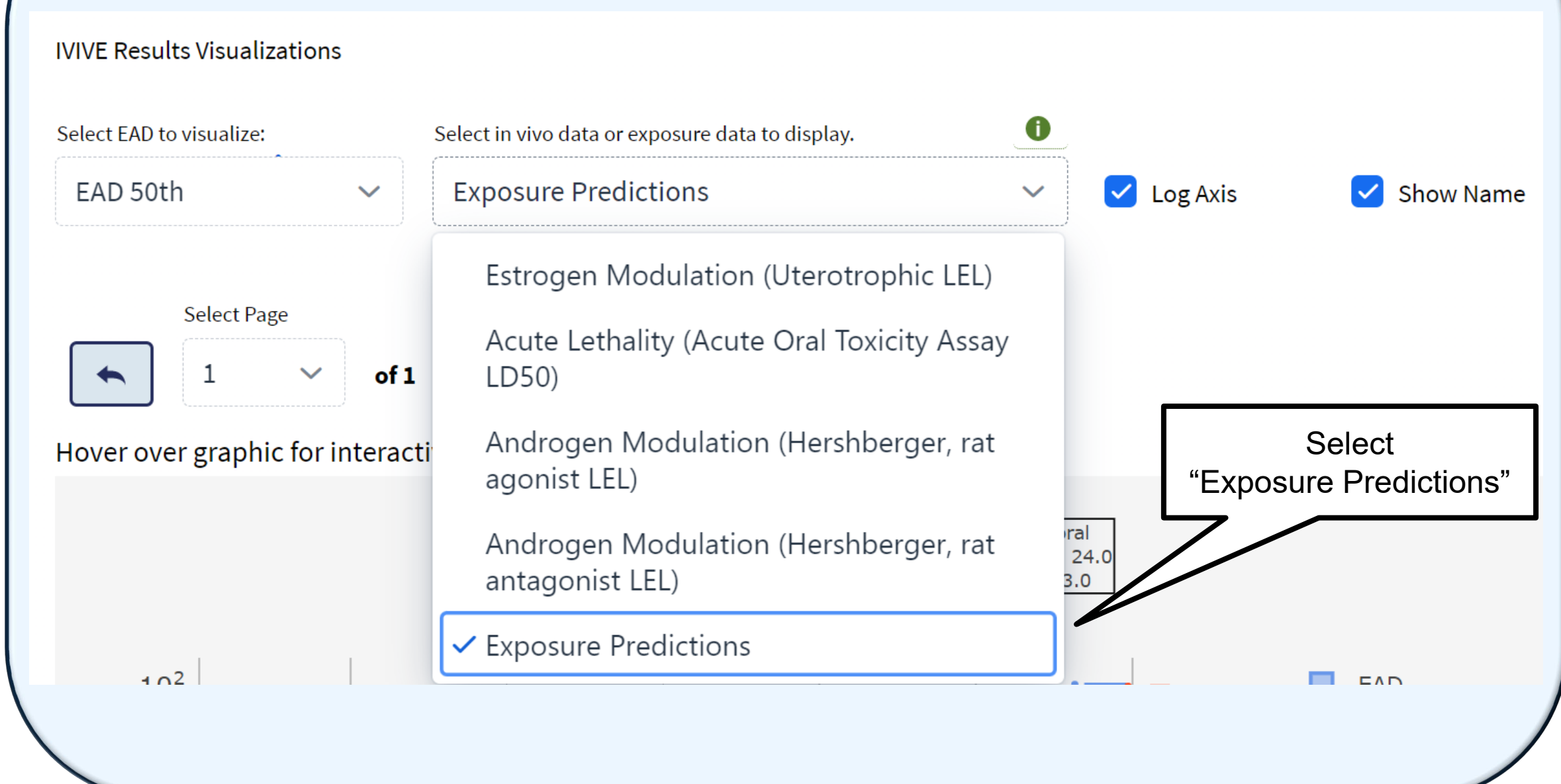

Exposure Predictions through Search Tool

- Exposure predictions are also added as an overlay option for visual comparison against the EAD estimates from the IVIVE tool.

$$C_{ss} = \frac{Dose}{CL_r + CL_h}$$

Step 1 to Apply IVIVE Overlay: Parameterize IVIVE models for select chemicals and assays

The IVIVE tool uses pharmacokinetic models to predict the equivalent administered dose (EAD) from the activity concentration of selected assays.

Use 24-hour dosing interval so EAD units will match exposure units of mg/kg/day.

A three-compartments P4 model for Cmax from the US EPA httk package. For details see User Guide.

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

Select "Exposure Predictions"

Step 3 to Apply IVIVE Overlay: Visualize exposure predictions

95th percentile
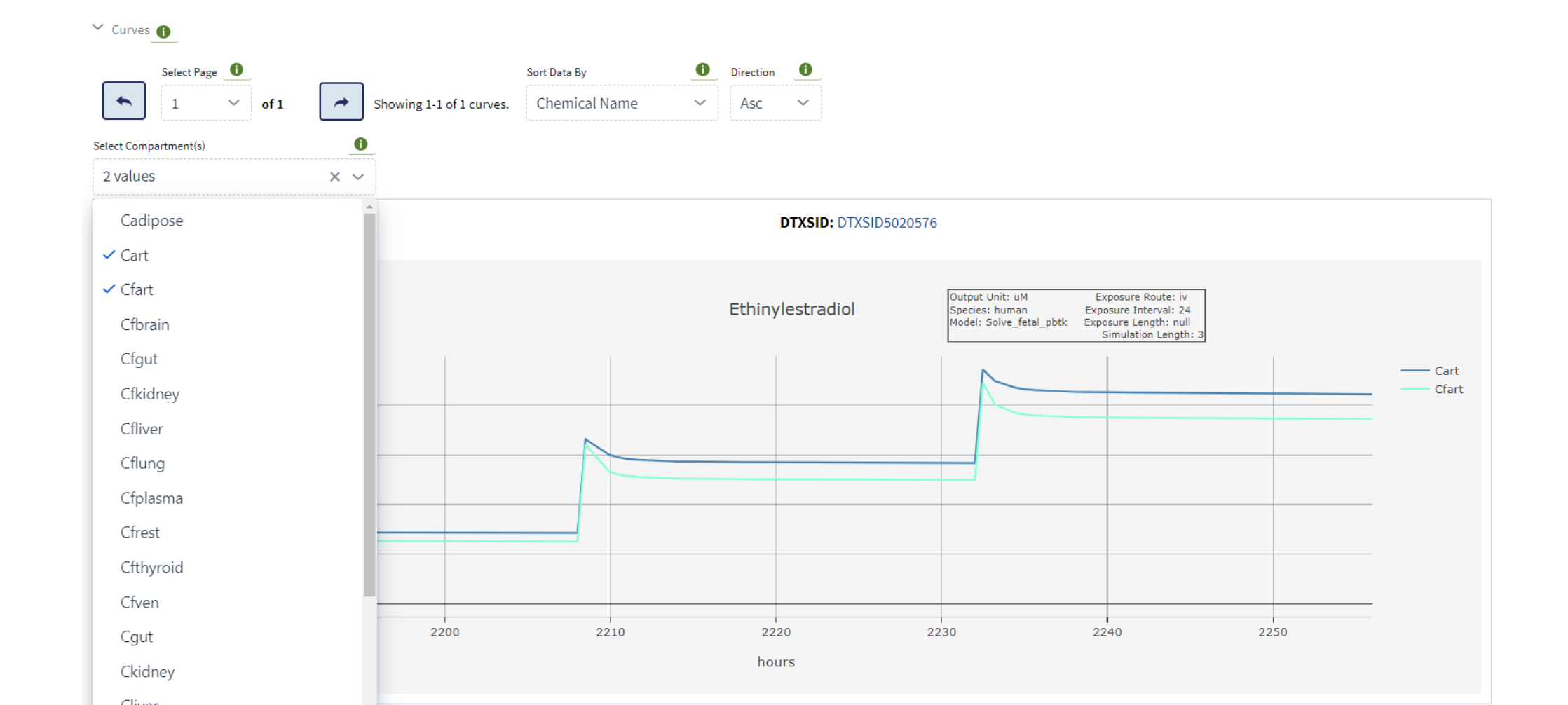Median
5th percentile
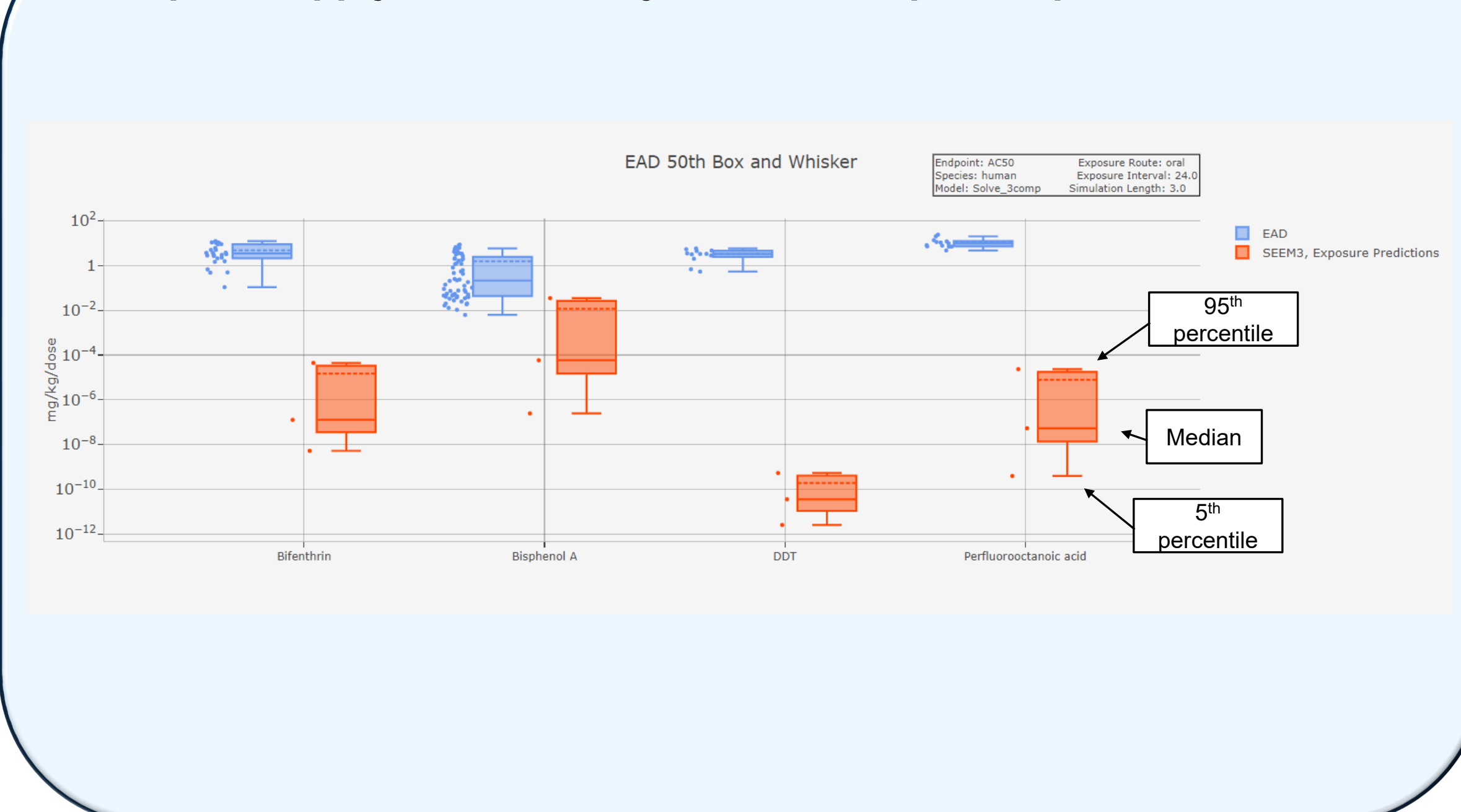
PBPK Gestational Model

- The ICE PBPK tool can utilize either experimental data or predicted parameters 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.
- The 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).

Body weight of the simulated subject in kg. Default is 70 kg for human.

The gestation day when exposure starts. Default is day 91. The range of selection can be 91 to 280 days (13 to 40 weeks).
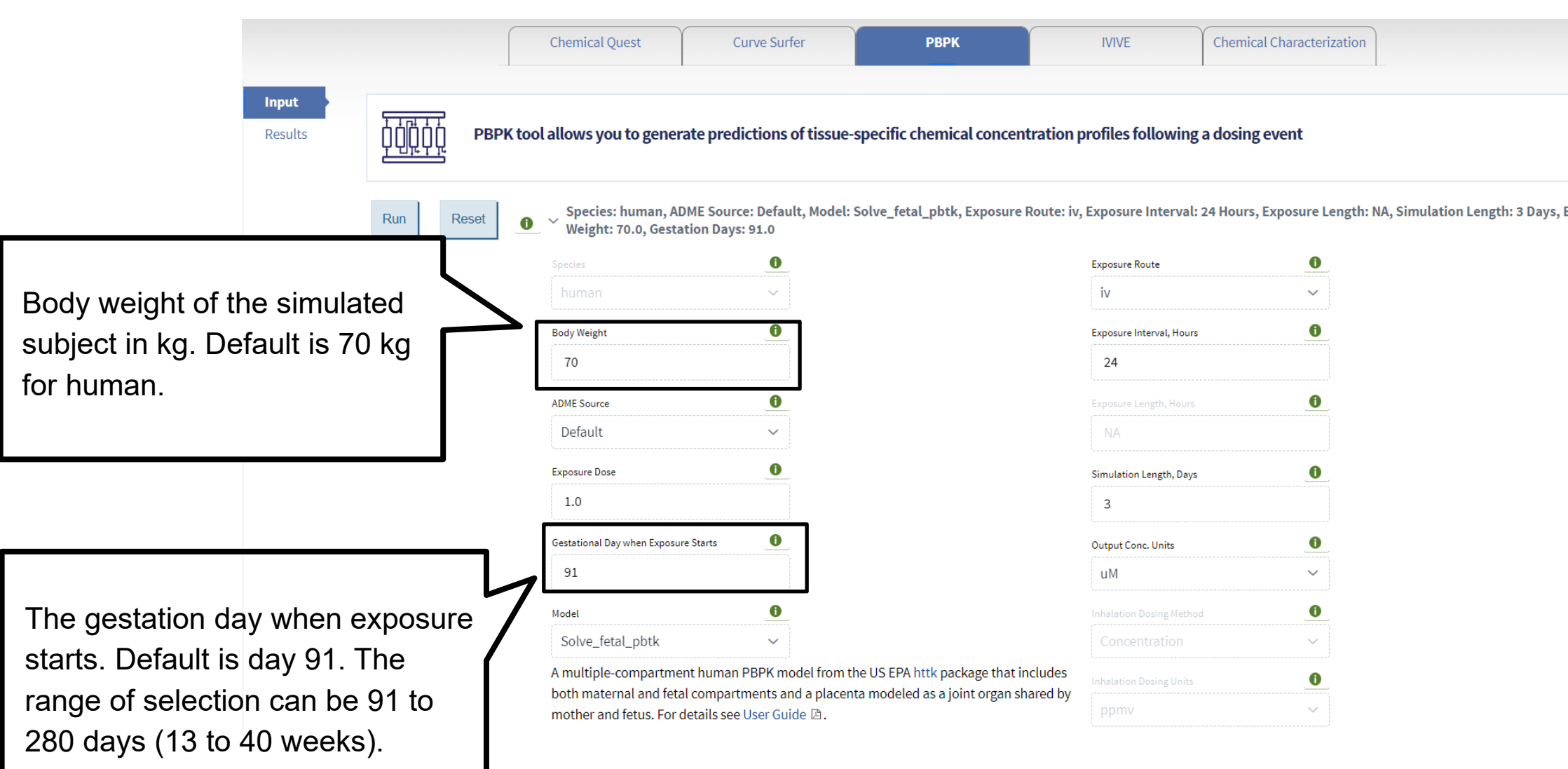
- Output provides filtering options to compare concentration-time profiles in various fetal and maternal compartments.

- 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.
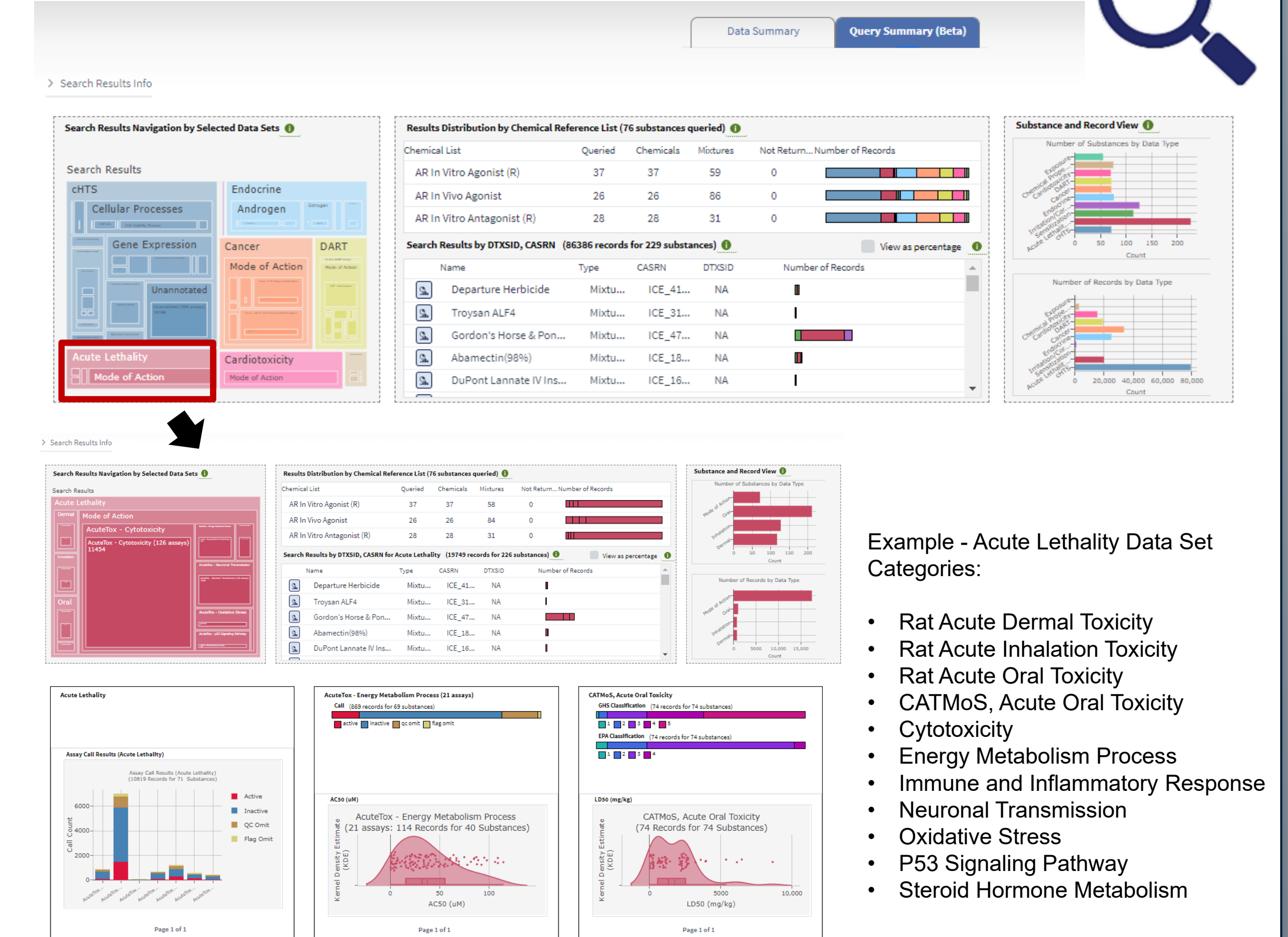

IVIVE Gestational Model

- 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 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.

$$C_{ss} = \frac{Dose}{CL_r + CL_h}$$

Search Results Redesign (Beta)

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

Example - Acute Lethality Data Set Categories:
- Rat Acute Dermal Toxicity
- Rat Acute Inhalation Toxicity
- Rat Acute Oral Toxicity
- CATMoS, Acute Oral Toxicity
- Cytotoxicity
- Energy Metabolism Process
- Immune and Inflammatory Response
- Neuronal Transmission
- Oxidative Stress
- P53 Signaling Pathway
- Steroid Hormone Metabolism

- Data availability is summarized for each individual substance and each Chemical Quick List. Color bars show 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.

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.
- Functional Use Explorer within the ICE Chemical Characterization tool provides visualizations of functional use data with the help of heat maps. The categories represented describe the known or predicted role of a chemical in a product.
- 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 SEEM3 predicted exposures.
- 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.
- New Search results page provides summary visualizations to help users contextualize and interactively explore data to identify relevant outputs optimized for the user's specific needs.

References

Daniel AB et al. 2022. Data curation to support toxicity assessments using the Integrated Chemical Environment. Front Toxicol. 4:987848. https://doi.org/10.3389/ftox.2022.987848

Kapraun DF et al. 2022. Evaluation of a rapid, generic human gestational dose model. Reprod Toxicol. 113:172-188. https://doi.org/10.1016/j.reprotox.2022.09.004. Epub 2022 Sep 16. PMID: 36122840; PMCID: PMC9761697.

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Acknowledgments and More Information