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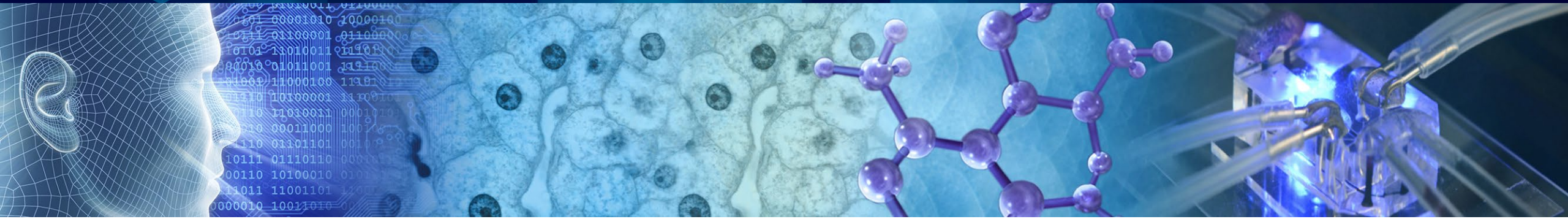

The Integrated Chemical Environment (ICE): An open-access tool to support chemical evaluations

Victoria Hull, M.S.
Inotiv, Inc., Contractor Supporting the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

SACATM 2023

Disclaimer: Inotiv staff provide technical support for NICEATM, but do not represent NIEHS, NTP, or the official positions of any federal agency.

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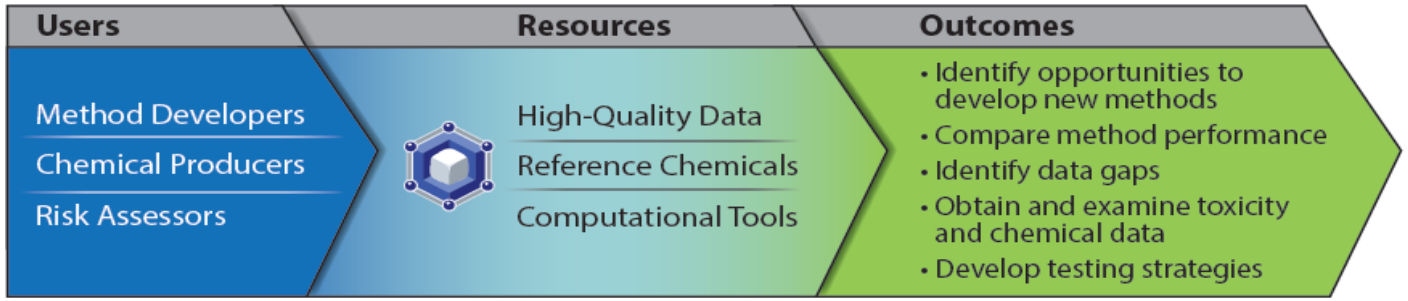
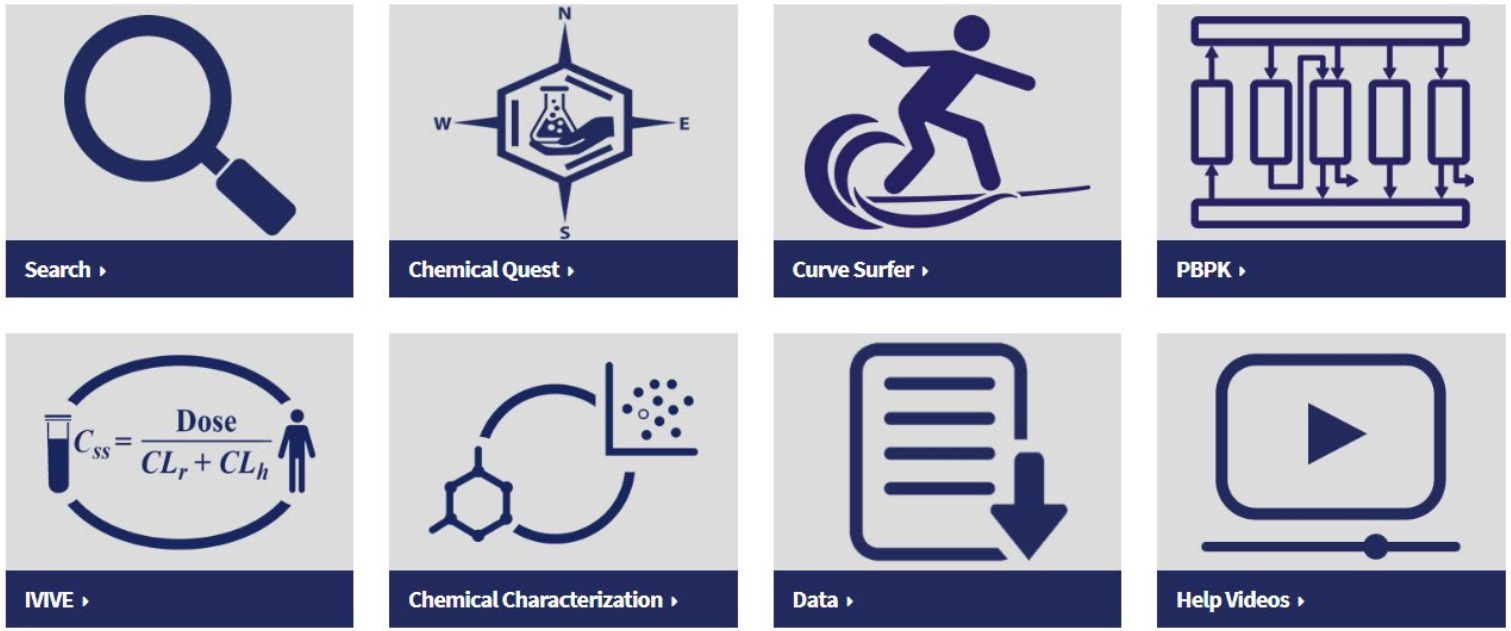
ICE: The Integrated Chemical Environment

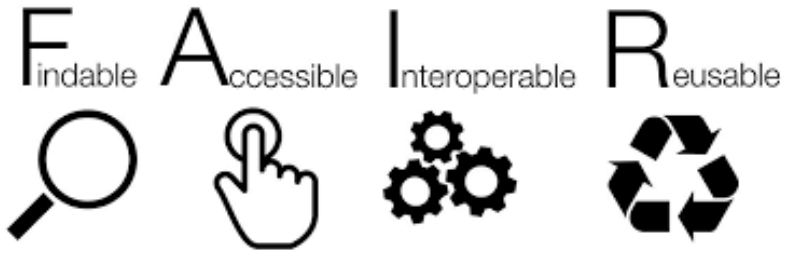
Integrated Chemical Environment



Releases in 2023:

ICE v4.0 (March)
ICE v4.0.1 (August)



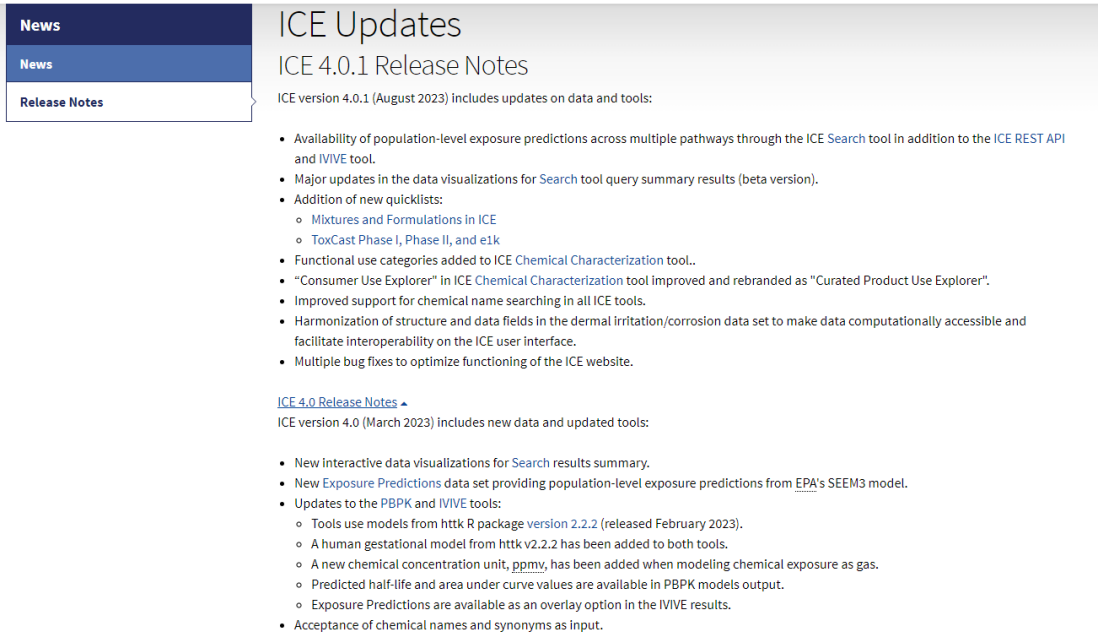


Bell et al. 2017 EHP
Bell et al. 2020 Tox In Vitro
Abedini et al. 2021 Comp Tox
Daniel et al. 2022 Front Toxicol

https://ice.ntp.niehs.nih.gov/

Accessing ICE Data and Tools

https://ice.ntp.niehs.nih.gov/



- ICE Database Access via REST API
  - https://ice.ntp.niehs.nih.gov/api/v1/search
  - For one or more chemical ids, return a list of Assay/Endpoint objects

Data

Updated in Releases v4.0 and v4.0.1

ICE Data (In Vivo and In Vitro)

Toxicity endpoint	Assays	# of chemicals
Chemical Parameters	Experimental physicochemical properties	~20000
ADME Parameters	Fu, intrinsic clearance, Caco2 permeability	~3000
Acute Toxicity	In vivo acute oral, dermal, and inhalation toxicity	~10000
Cancer	In vivo and in vitro cancer, and Weight of Evidence	3038
DART	In vivo and in vitro DART	628
Skin Sensitization	In vivo and in vitro skin sensitization	1771
Skin Irritation	In vivo and in vitro skin irritation/corrosion	595
Eye Irritation	In vivo and in vitro eye irritation/corrosion	455
Endocrine	In vivo and low throughput in vitro data on AR and ER agonist and antagonist activity	384
cHTS	Curated US EPA's ToxCast and Federal Tox21 assays (In vitro)	~10000

Harmonized and updated datasets!

Data

Updated in Releases v4.0 and v4.0.1

ICE Data (In Silico Models/Integrated Approaches)

Endpoint	Model	# of chemicals
Physicochemical Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Structural Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Predicted ADME Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Environmental Fate	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Acute Oral Toxicity	Collaborative Acute Toxicity Modeling Suite (CATMoS) - Rat acute oral toxicity. Mansouri et al. EHP 2021	1M+
Endocrine	Estrogen Receptor pathway Model. Browne et al. ES&T 2015	1812
	Androgen Receptor Pathway Model. Kleinstreuer et al. Chem Res Tox 2017	1855
	Collaborative Estrogen Receptor Activity Prediction Project (CERAPP). Mansouri et al. EHP 2016	1M+
	Collaborative Modeling Project for Androgen Receptor Activity (COMPARA). Mansouri et al. EHP 2020	1M+
Exposure Predictions	Systematic Empirical Evaluation of Models (US EPA'S SEEM3). Ring et al. Environ Sci Technol 2019	475,000+

New exposure predictions!

Updated in Release v4.0.1

ICE Chemical Quick Lists

Reference Chemical List
AR In Vitro Agonist
AR In Vitro Antagonist
ER In Vivo Agonist
ER In Vitro Agonist
Eye Irritation-Corrosion
Genotoxicity
OECD Defined Approach to Skin Sensitization: Human
OECD Defined Approach to Skin Sensitization: LLNA
Skin Corrosion

Non-reference Chemical List
AR In Vivo Agonists
AR In Vivo Antagonists
EPA Pesticide Active Ingredients
EPA Pesticide Inert Ingredients, Food and Nonfood Use
EPA IRIS Cancer Assessment
EPA IRIS Non-Cancer Assessment
IARC Classifications
Mixtures and Formulations in ICE
NTP Cancer Bioassay Chemicals
RoC Classifications
Steroidogenesis - Androgen
Steroidogenesis - Estrogen
Thyroid
Tox21
ToxCast Phase I, Phase II, and e1k

New quick lists!

ICE Tools Workflow

Integrated Chemical Environment

Perform a search	Expand inventory: Identify similar chemicals	Characterize chemical inventory	Review in vitro data details	Generate chemical concentration predictions	Predict equivalent administered dose from in vitro data
Search	Chemical Quest	Chemical characterization	Curve Surfer	PBPK	IVIVE

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Search

Search: Updated in Releases v4.0 and v4.0.1

Perform a search → Identify similar chemicals → Characterize chemical inventory → Review in vitro data details → Generate chemical concentration predictions → Predict equivalent administered dose

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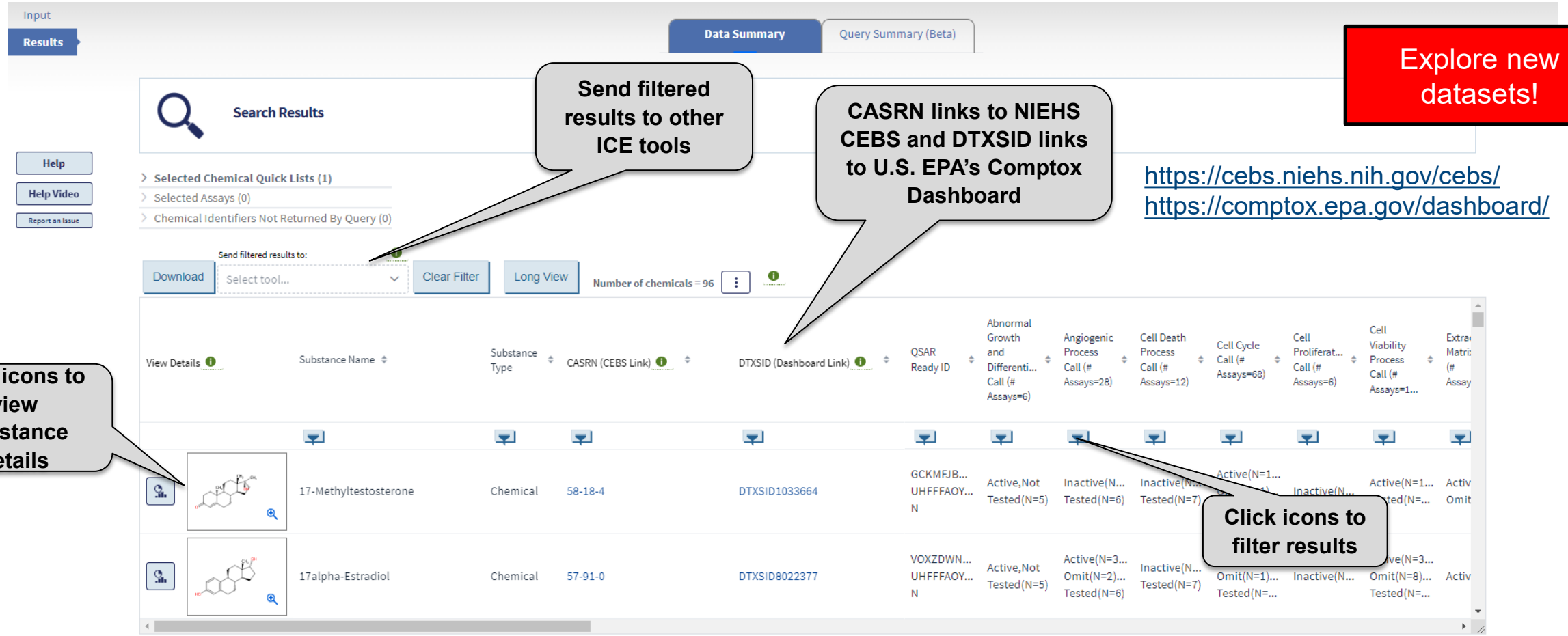
Search

Search: Updated in Releases v4.0 and v4.0.1

Perform a search → Identify similar chemicals → Characterize chemical inventory → Review in vitro data details → Generate chemical concentration predictions → Predict equivalent administered dose



Send filtered results to other ICE tools

CASRN links to NIEHS CEBS and DTXSID links to U.S. EPA's Comptox Dashboard

Explore new datasets!

https://cebs.niehs.nih.gov/cebs/
https://comptox.epa.gov/dashboard/

Click icons to view substance details

Click icons to filter results

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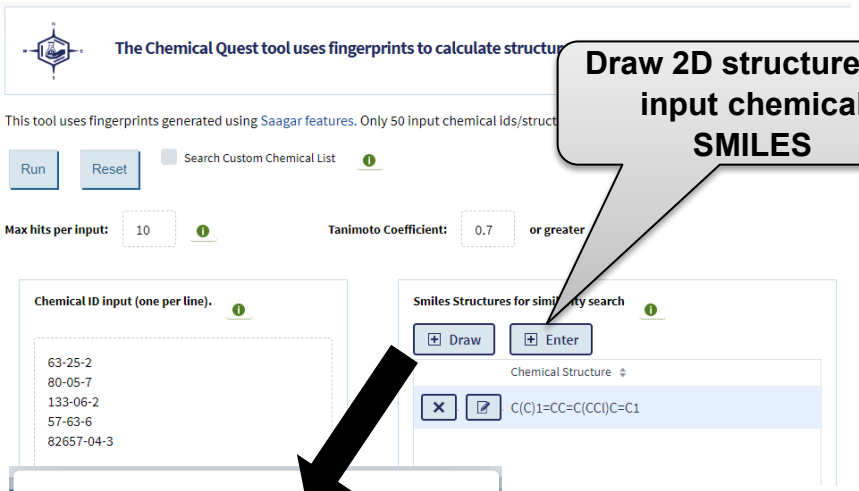
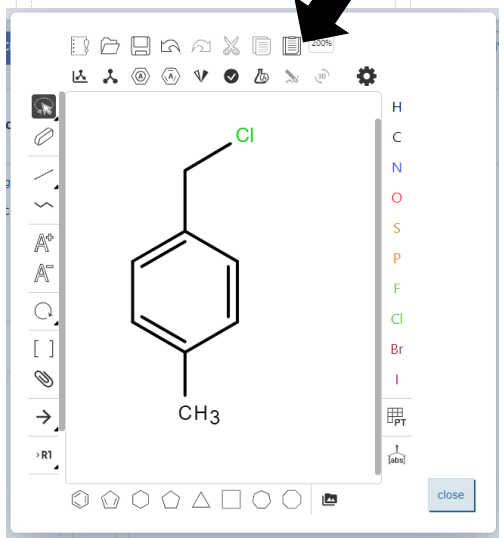
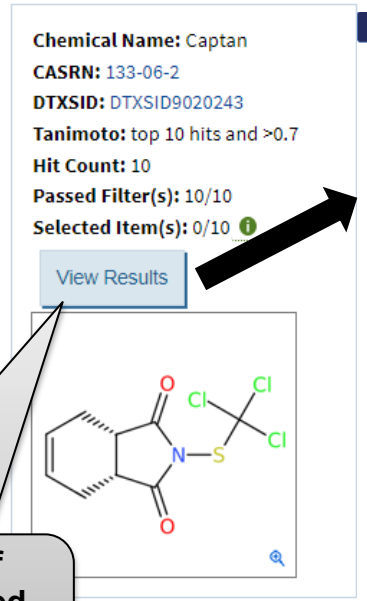
Chemical Quest

Perform a search → **Expand Inventory: Identify similar chemicals** → Characterize chemical inventory → Review in vitro data details → Generate chemical concentration predictions → Predict equivalent administered dose

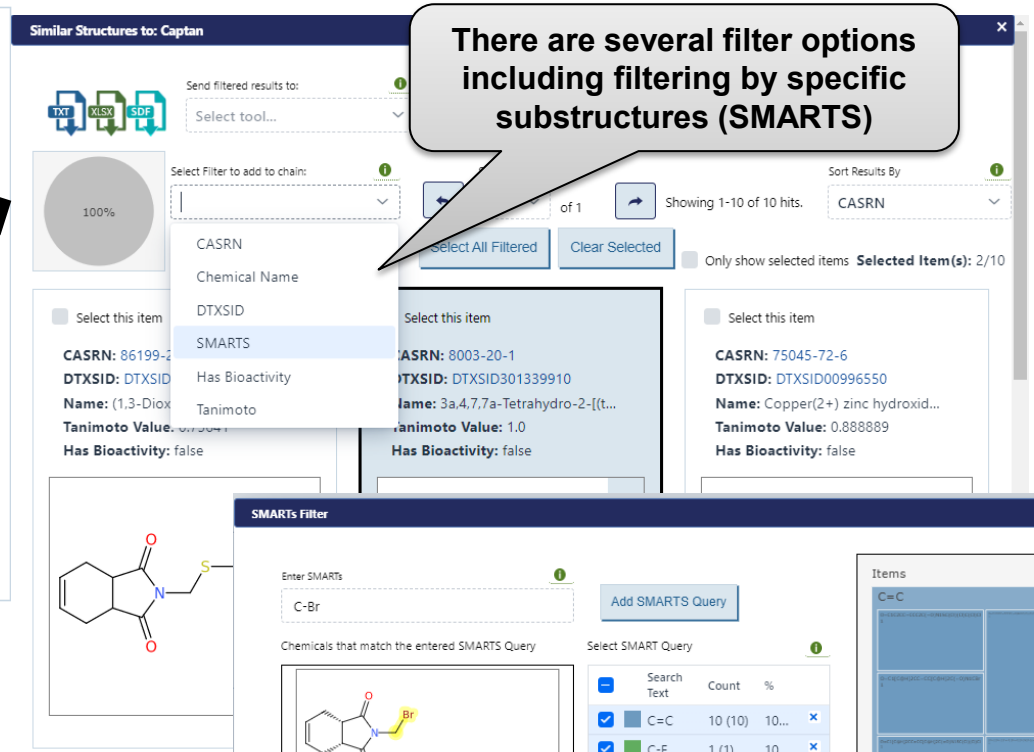


Draw 2D structures or input chemical SMILES

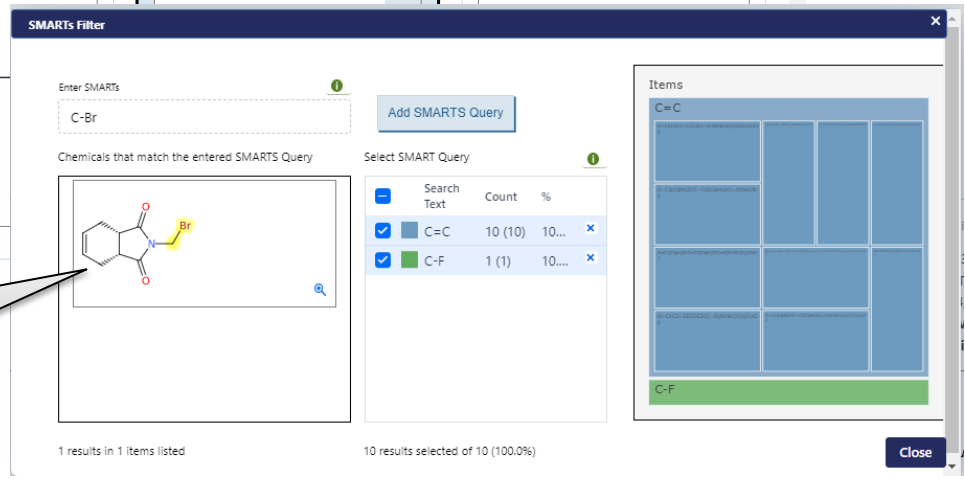




Results show number of similar structures identified for each input chemical or structure



There are several filter options including filtering by specific substructures (SMARTS)



When specifying SMART strings, the substructure will be highlighted for easy identification

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Chemical Characterization

Chemical Characterization: Updated in Release 4.0.1

Perform a search → Identify similar chemicals → **Characterize chemical inventory** → Review in vitro data details → Generate chemical concentration predictions → Predict equivalent administered dose

Chemical Properties Summary

Values displayed are Open Structure-Activity/Property Relationship App (OPERA) predictions:

Lists: Both Chemical Lists

Users can input one or two lists of chemicals and toggle results to show one or both lists

Send filtered results to: Select tool...

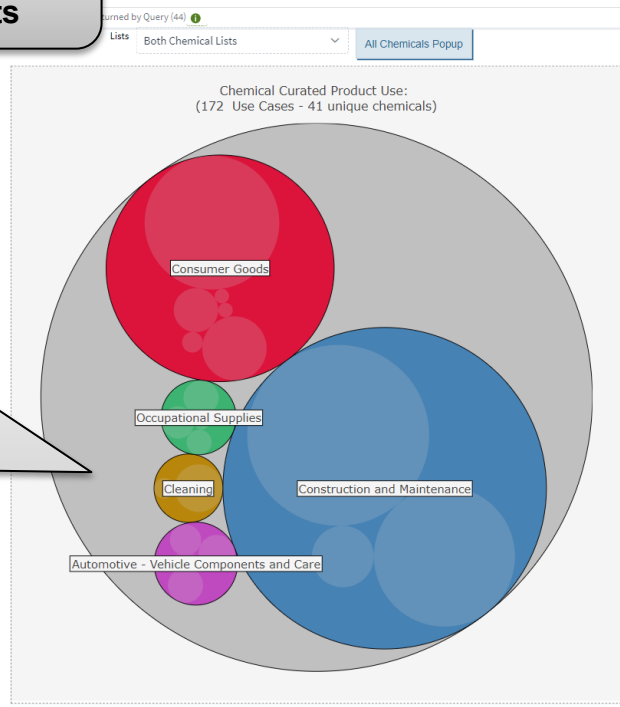
Chemical List (OPERA) Predictions by Input List, CASRN

List	Substance Name	CASRN (CEBS Link)	DTXSID (Dashboard Link)	Molecular Weight, g/mol	OPERA, Boiling Point, C	OPERA, Henry's Law Constant, atm-m3/mol
Custom Chemical List 1	Carbaryl	63-25-2	DTXSID9020247	201.221	314.943	-7.86
Custom Chemical List 1	Captan	133-06-2	DTXSID9020243	300.589	302.104	-5.43
Custom Chemical List 1	(+)-cis-Permethrin	54774-45-7	DTXSID5052208	391.288	401.446	-7.62

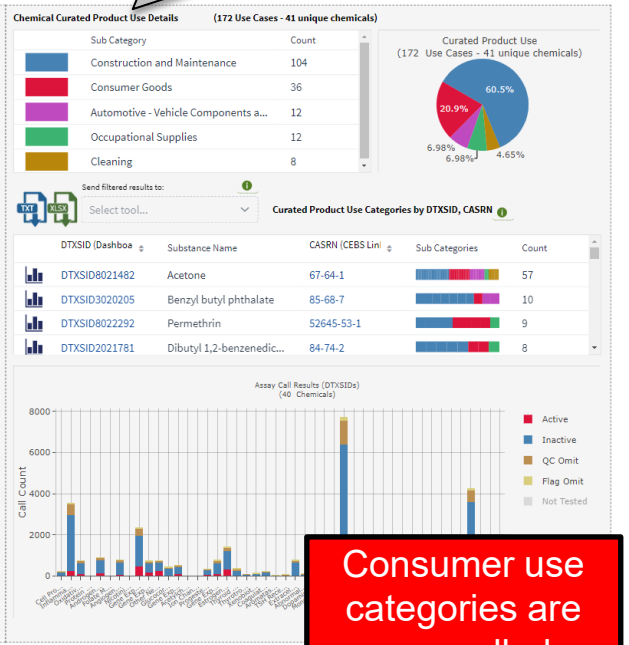
Chemical List Statistical Summary of (OPERA) Predictions

Endpoint	Min	25th	Median	Mean	75th	Max
OPERA, Water Solubility, log10, moles/L	-10.4	-4.35	-2.33	-2.81	-0.869	1.355
Molecular Weight, g/mol	30.026	120.17	197.446	214.652	268.352	1202.611
OPERA, Octanol-Air Partition Coefficient, KOA log10	0.969	3.854	7.843	6.883	9.383	11.757

Nested bubble graphs show curated product use categories derived from EPA's Chemicals and Products Database (CPDat)



Summary details show product use details by category and by chemical



Consumer use categories are now called curated product use categories!

OPERA v2.8 (Mansouri et al., 2018)

CPDat v3 (Williams, 2017)

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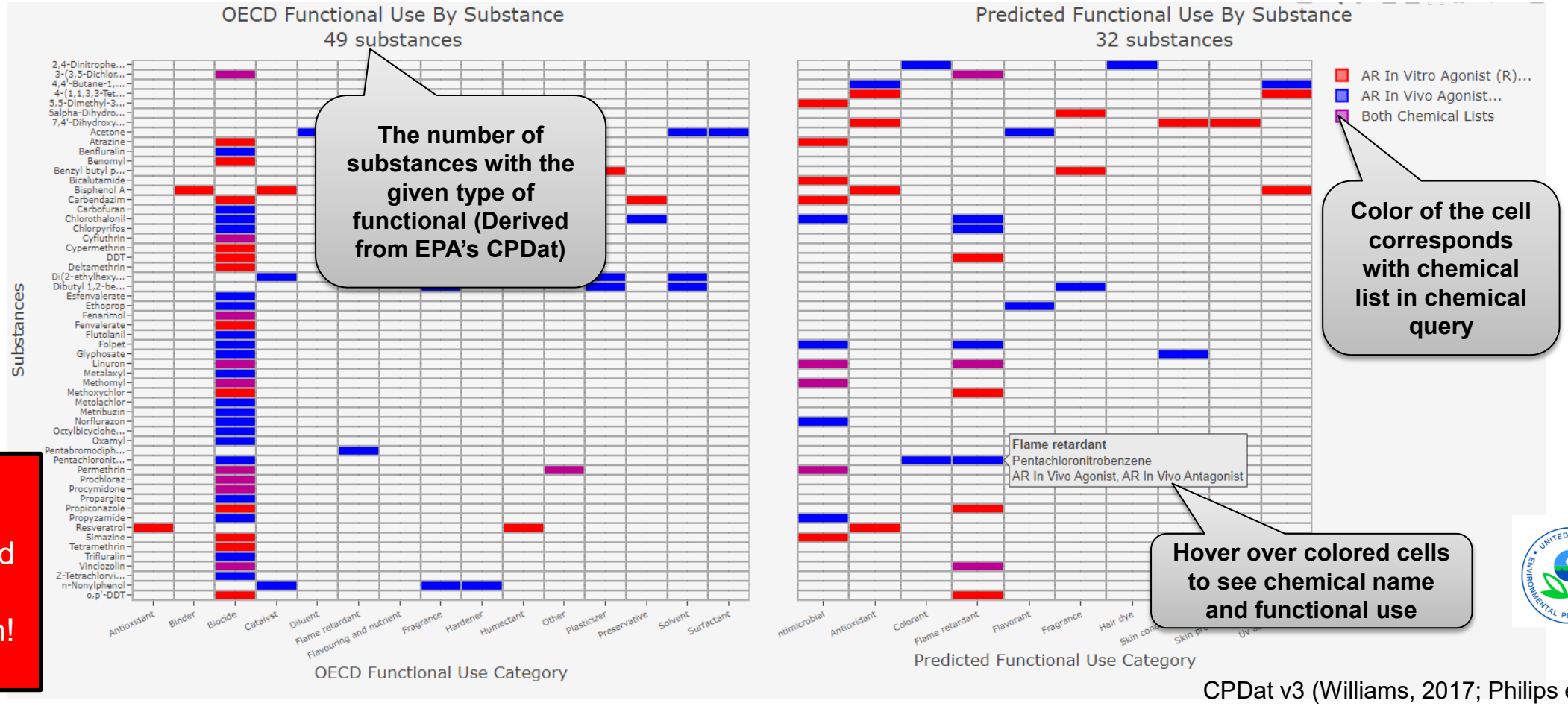
Chemical Characterization

Chemical Characterization: New in Release 4.0.1

Perform a search → Identify similar chemicals → **Characterize chemical inventory** → Review in vitro data details → Generate chemical concentration predictions → Predict equivalent administered dose



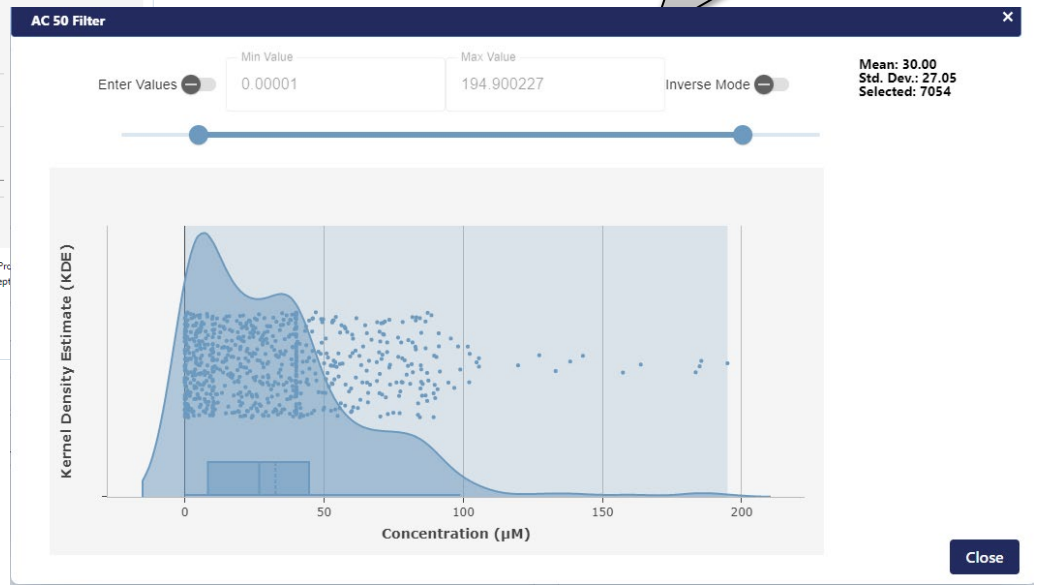
New use category and heatmap visualization!

CPDat v3 (Williams, 2017; Philips et al. 2018)

Perform a search | Identify similar chemicals | Characterize chemical inventory | **Review cHTS concentration-response curves** | Generate chemical concentration predictions | Predict equivalent administered dose

to filter based on ssay, assay target, c.

View data breakdown by filter terms and see selection highlighted



Plots have key features highlighted and details for assay and chemical information are provided below plots

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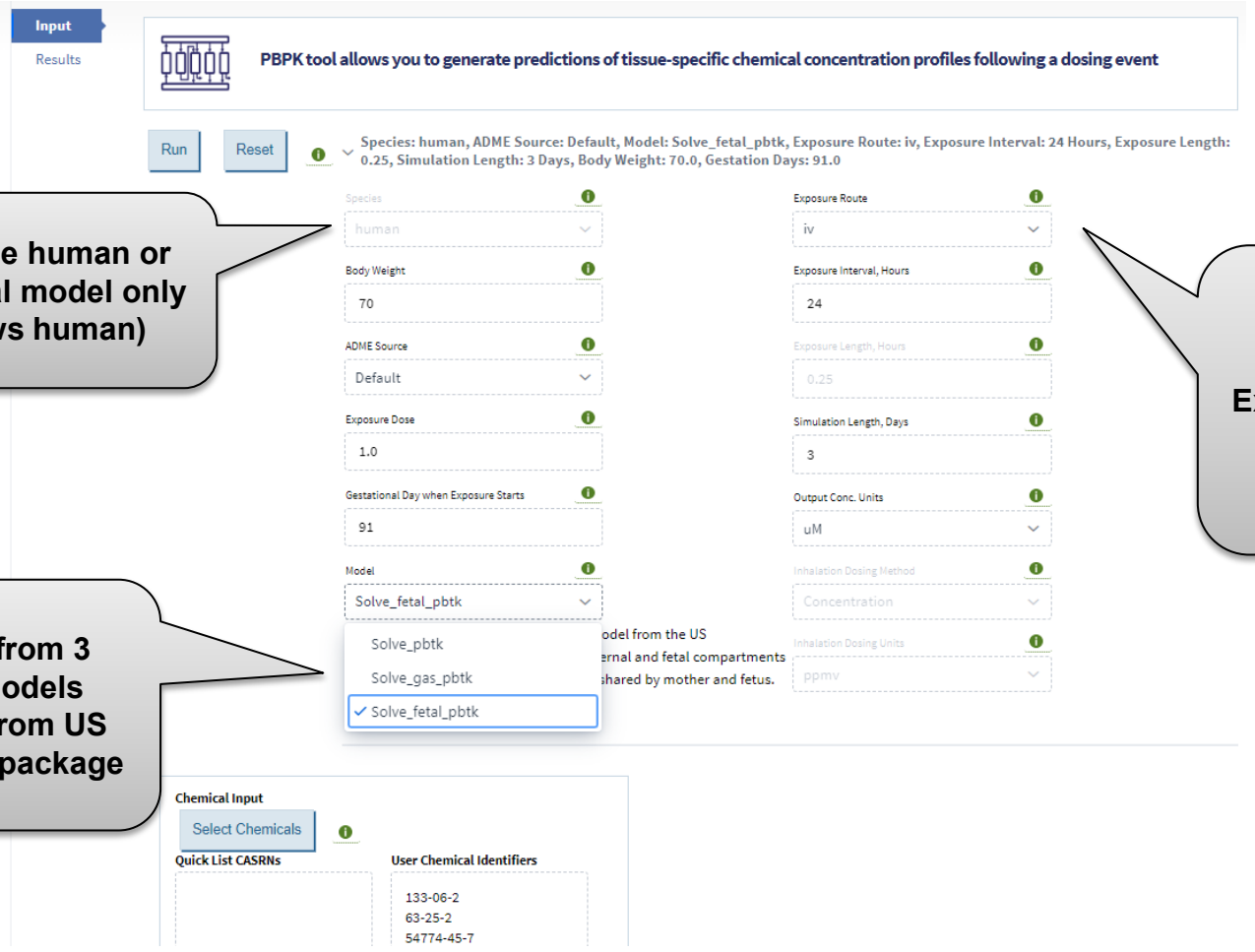
PBPK

PBPK: Updated in Release v4.0

Perform a search → Identify similar chemicals → Characterize chemical inventory → Review in vitro data details → **Generate chemical concentration predictions** → Predict equivalent administered dose

Updated version of httk! New fetal pbtk model! Inhalation model now accepts concentration units of ppmv!



Choose human or rat (fetal model only allows human)

Customize model parameters such as Exposure Route, Exposure Length, and Simulation Length

Choose from 3 PBPK models sourced from US EPA's httk package

httk v2.2.2 (Pearce et al., 2017)

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PBPK

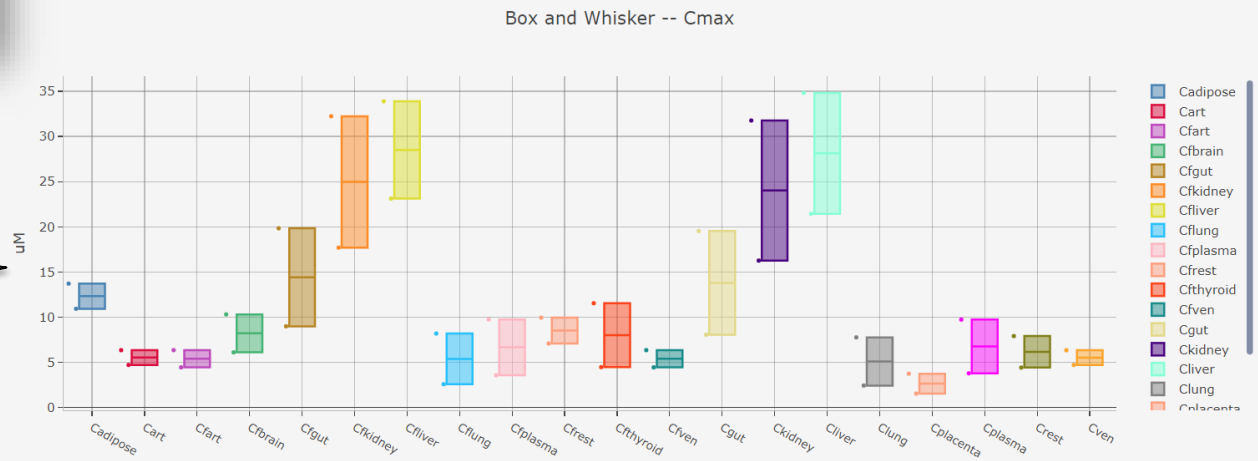
PBPK: Updated in Release v4.0

Perform a search → Identify similar chemicals → Characterize chemical inventory → Review in vitro data details → **Generate chemical concentration predictions** → Predict equivalent administered dose

For each input chemical, the results show the concentration of the chemical over time in plasma and each tissue compartment

Visualize fetal and maternal tissue concentrations!

Boxplots show the Cmax distribution across all returned chemicals for each compartment



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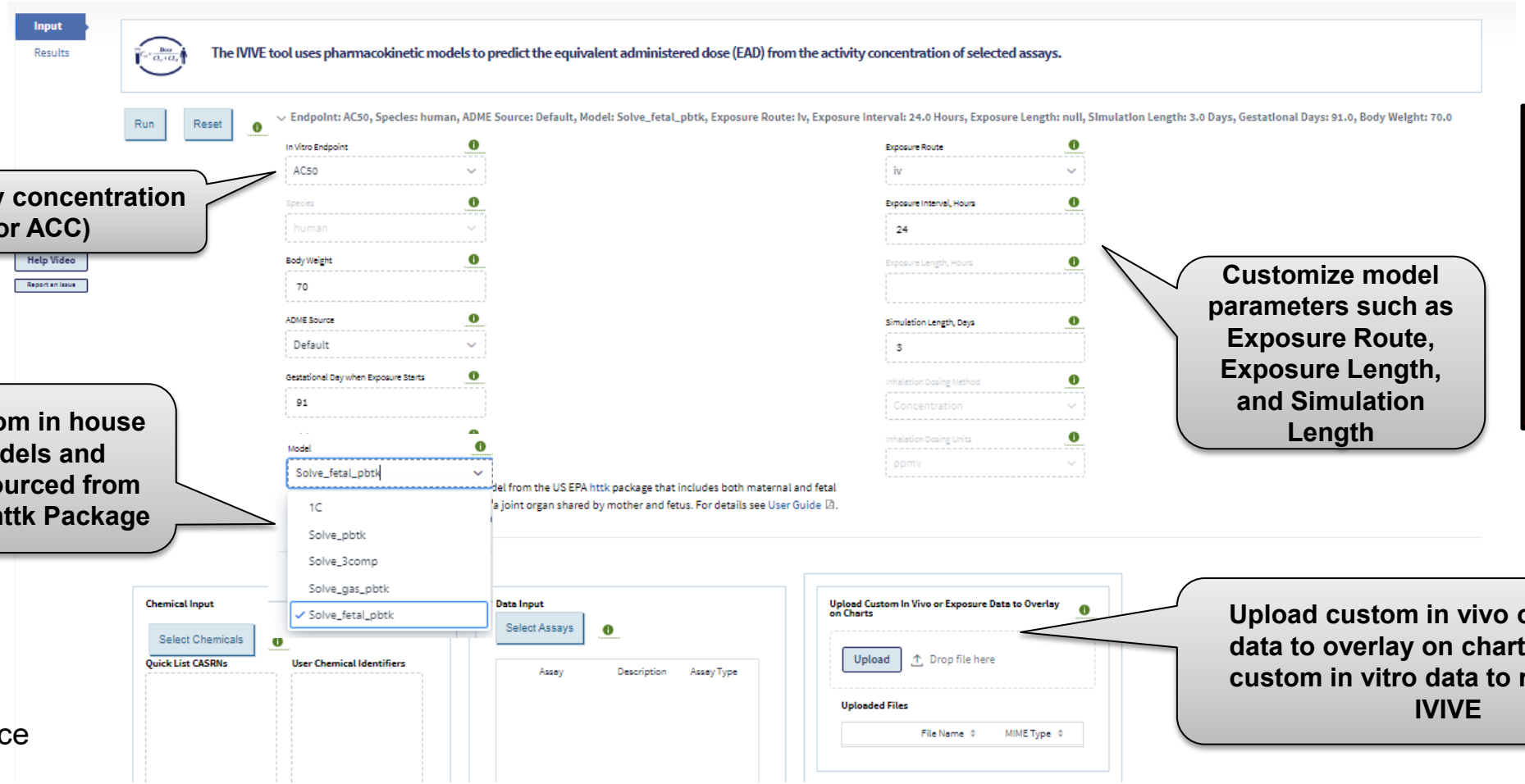
IVIVE

IVIVE: Updated in Release v4.0

Perform a search → Identify similar chemicals → Characterize chemical inventory → Review in vitro data details → Generate chemical concentration predictions → **Predict equivalent administered dose from in vitro data**



Type of activity concentration (AC50 or ACC)

Choose from in house ICE models and models sourced from US EPA's httk Package

Customize model parameters such as Exposure Route, Exposure Length, and Simulation Length

New fetal pbtk model! Inhalation model now accepts concentration units of ppmv!

Upload custom in vivo or exposure data to overlay on charts or upload custom in vitro data to run through IVIVE

httk v2.2.2 (Pearce et al., 2017)

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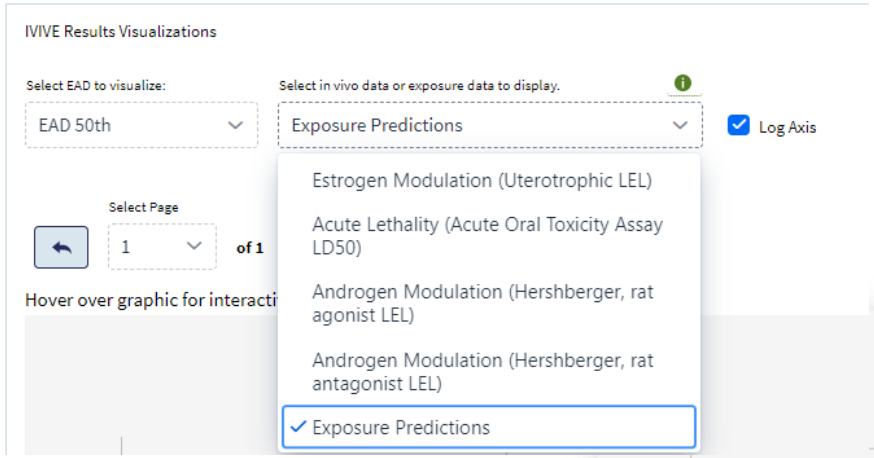
IVIVE

IVIVE: Updated in Release v4.0

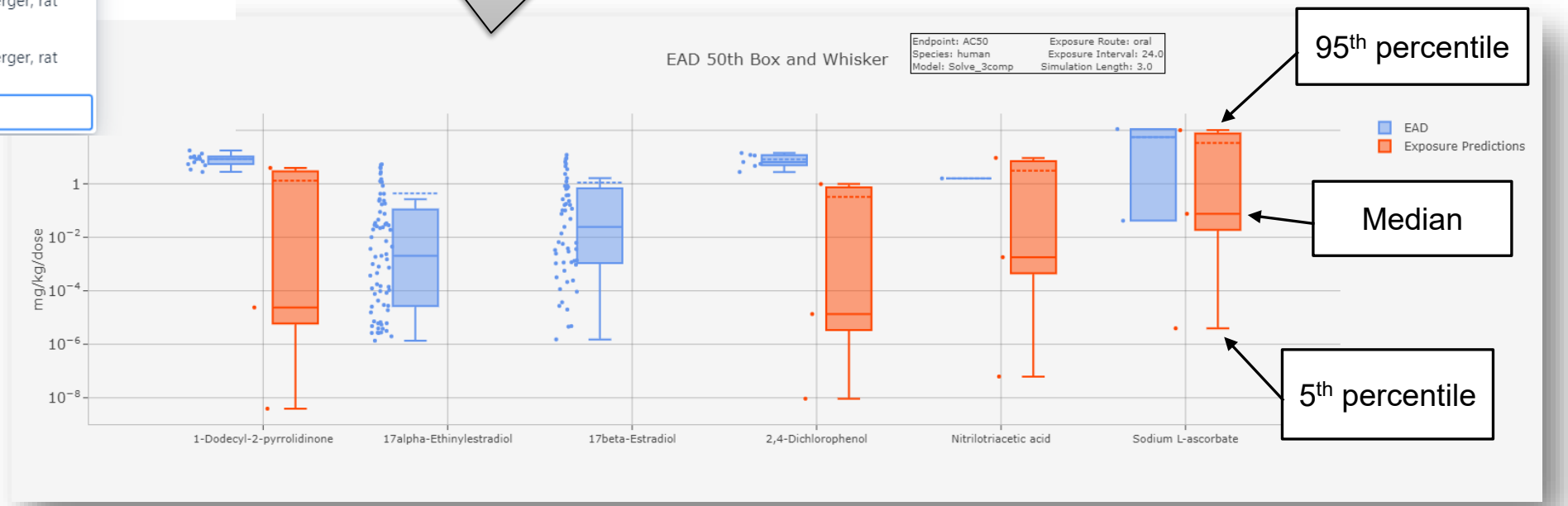
Perform a search → Identify similar chemicals → Characterize chemical inventory → Review in vitro data details → Generate chemical concentration predictions → **Predict equivalent administered dose from in vitro data**



Box and whisker plots show Equivalent Administered Dose (EAD) based on in vitro inputs

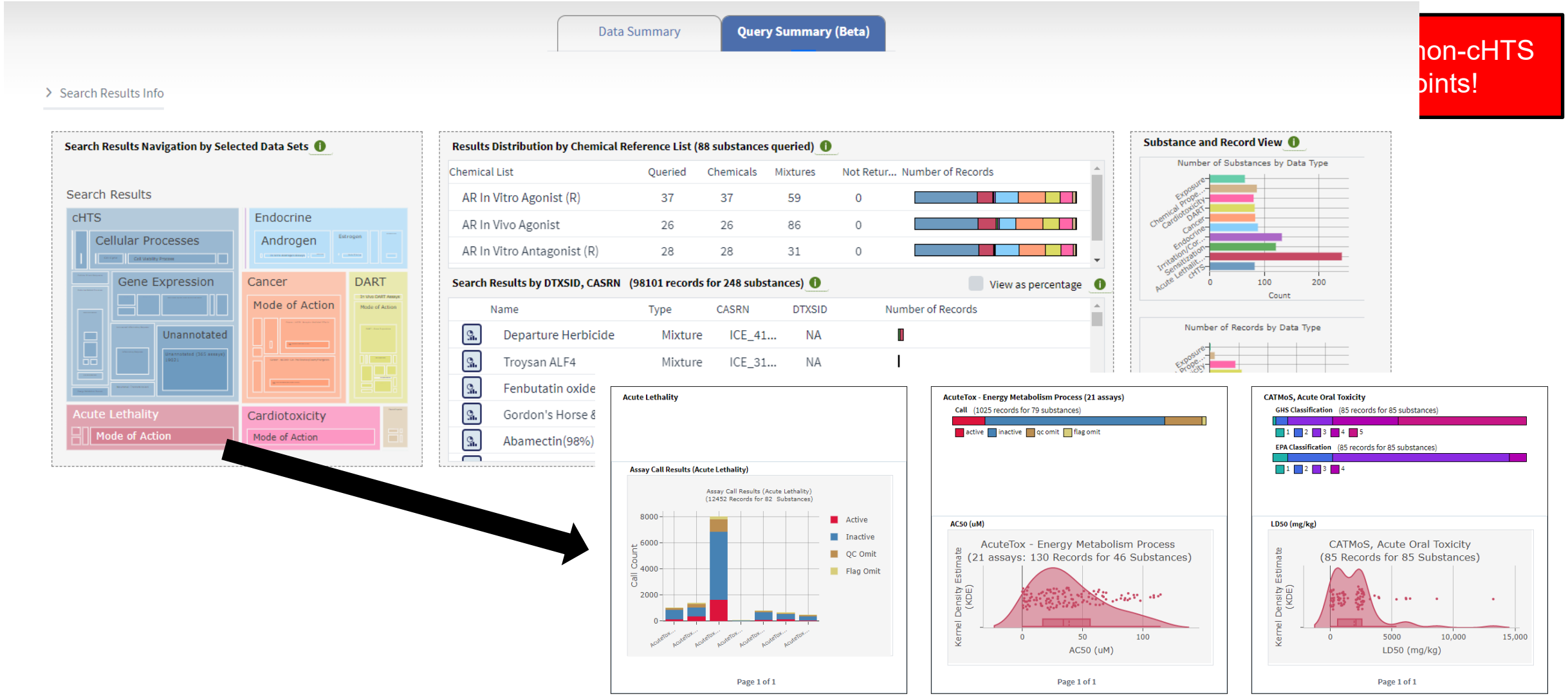
Overlay new exposure predictions!

Users can now overlay Exposure Predictions from EPA's SEEM3 model



SEEM3 (Ring et al., 2019)

Ongoing Additions – Search Query Summary Results (In Beta)



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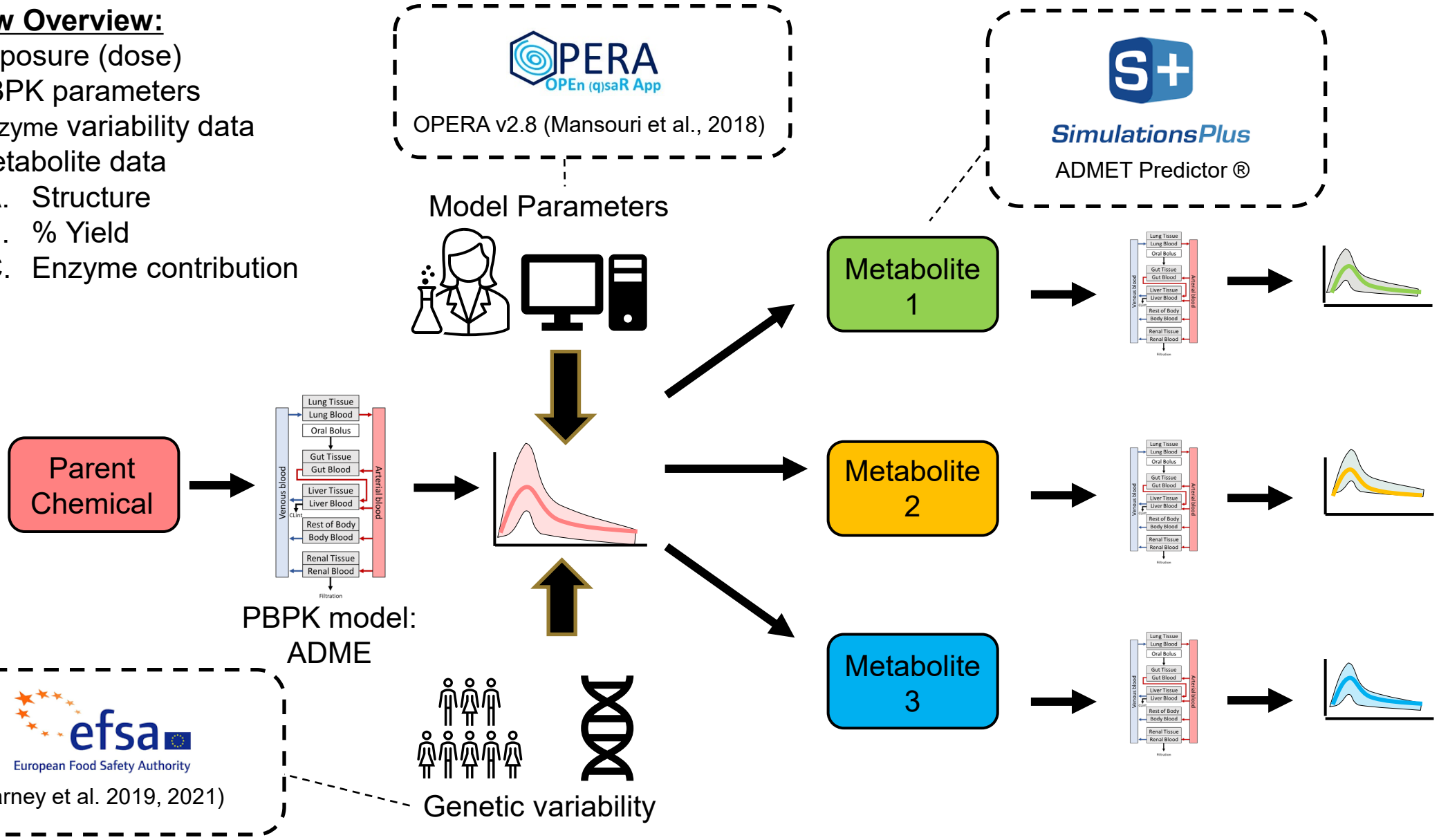
Future Additions – Genetic Enzyme Variability in PBPK Models

Workflow Overview:

1. Exposure (dose)
2. PBPK parameters
3. Enzyme variability data
4. Metabolite data
   A. Structure
   B. % Yield
   C. Enzyme contribution



Summary

- ICE is an open-access computational tool with highly-curated data and interoperable computational tools intended to support the development, application, and evaluation of New Approach Methodologies
- ICE is continuously updated to address evolving stakeholder needs. This includes, but is not limited to, the following updates released in 2023:
  - The ability to search using chemical names and synonyms
  - Population-level exposure predictions from EPA's SEEM3 model
  - Gestational models from EPA's httk package (v2.2.2) in PBPK and IVIVE tools
  - Functional use categories derived from EPA's Chemical and Products Database
  - New quick lists for mixtures and ToxCast chemicals
- Future updates will include the incorporation of additional endpoint specific visualizations and the integration of enzyme variability into PBPK models

Integrated Chemical Environment

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Acknowledgments

https://ice.ntp.niehs.nih.gov/

The NICEATM Group

Integrated Chemical Environment

https://github.com/NIEHS/OPERA

OPERA OPEn (q)saR App

https://www.sciome.com/

CEBS Chemical Effects in Biological Systems

https://cebs.niehs.nih.gov/cebs/

https://comptox.epa.gov/dashboard

Subscribe to NICEATM Newsemail list
https://ntp.niehs.nih.gov/go/niceatm