ICE Search Tool

Introduction

The ICE Search tool allows you to query toxicity endpoint, chemical property, and exposure data for chemicals and mixtures to get a summary view of available data. Summary tables of data and corresponding graphics can be viewed and filtered online or downloaded.

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 for a clearer field of vision.

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 make several videos available: the Input view video demonstrates how to build a query, and the Results view video explains how to interpret results.

If you encounter a problem using a tool, click the "Report an Issue" button on the left side of the display to generate an email to ICE Support. Click the “Cite ICE” button to view example citation formats for referencing ICE in your research publication that utilizes ICE data or outputs from ICE tools.

Building a Search Query

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

You must specify either chemicals or data sets to run a Search query.

- If you specify only chemicals, Search will return all available data for those chemicals.
- If you specify only a data set, Search will return all data available for that data set for all chemicals in ICE.

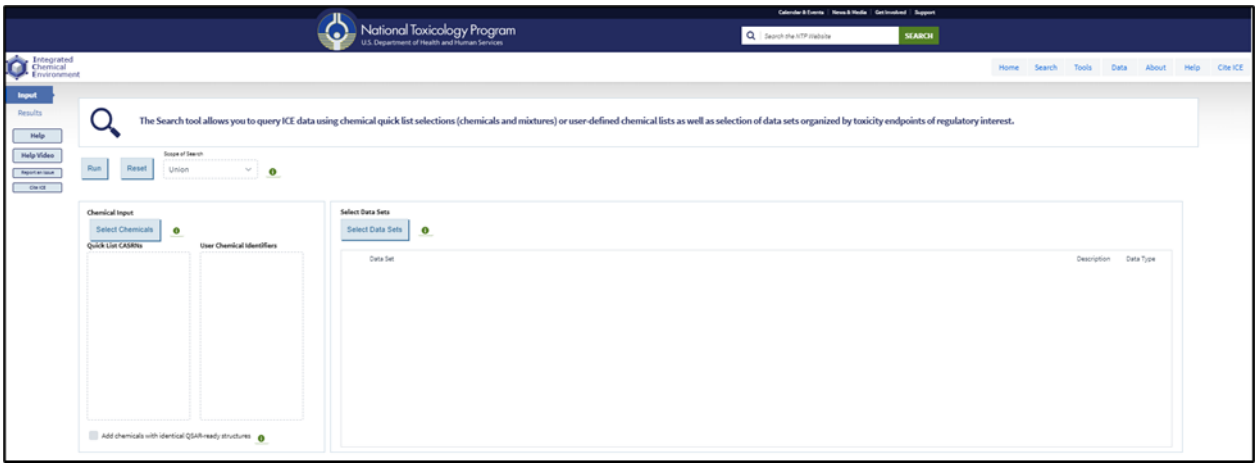

Figure 1. ICE Search tool Input view.

Chemical Input

The Chemical Input field on the left side of the Search Input view has two text boxes into which you can enter chemicals (**Figure 2**):

To populate the left-hand text box, select one or more ICE Chemical Quick Lists by clicking "Select Chemicals." In the dialog box that opens, select the checkboxes to choose one or more chemical lists. Click "Finished" when you are done. Chemical Abstracts Service Registry Numbers (CASRNs) from the selected ICE Chemical Quick Lists will populate the Quick List CASRNs text box.

- While in the dialog box, you can download ICE Chemical Quick Lists by clicking on the download icons to the right of the list names.
- Each download provides the list of chemicals along with additional metadata relevant to the Chemical Quick List.

To populate the right-hand text box, enter your own list of chemical identifiers, one per row. You can use any combination of the following identifiers:

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

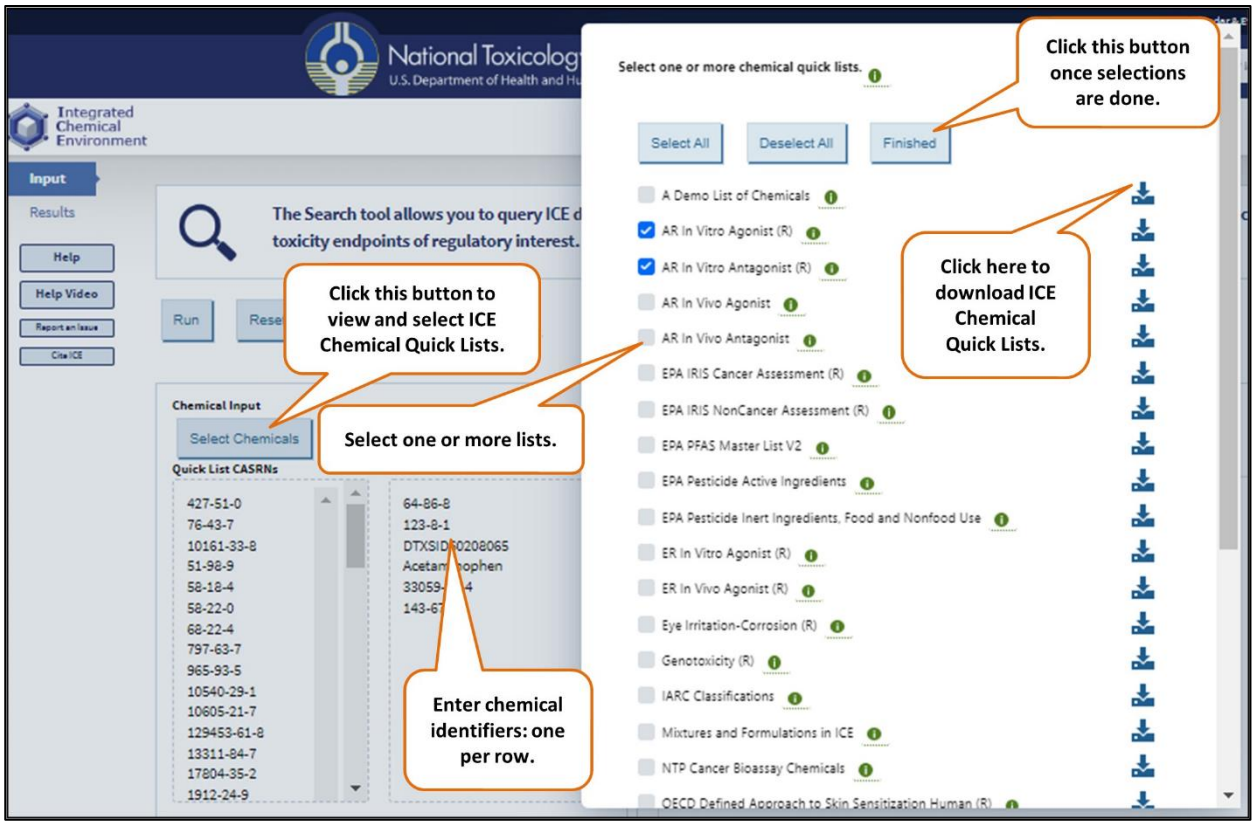

Figure 2. Input chemicals by typing chemical identifiers into the text box (right background) and/or selecting ICE Chemical Quick Lists (left background). Dialog box for selecting Chemical Quick Lists is in the foreground.

The two input boxes may contain some of the same chemicals.

The Search tool allows you to add chemicals with the same quantitative structure-activity relationship (QSAR) structure as chemicals in your query by selecting the checkbox at the bottom of the Chemical Input field (**Figure 3**). Selecting this box will add chemicals available in ICE to your query that have the same QSAR structure as a chemical you have specified, and, for example, will return results for salts and stereoisomers with the same QSAR structure as chemicals in your query.

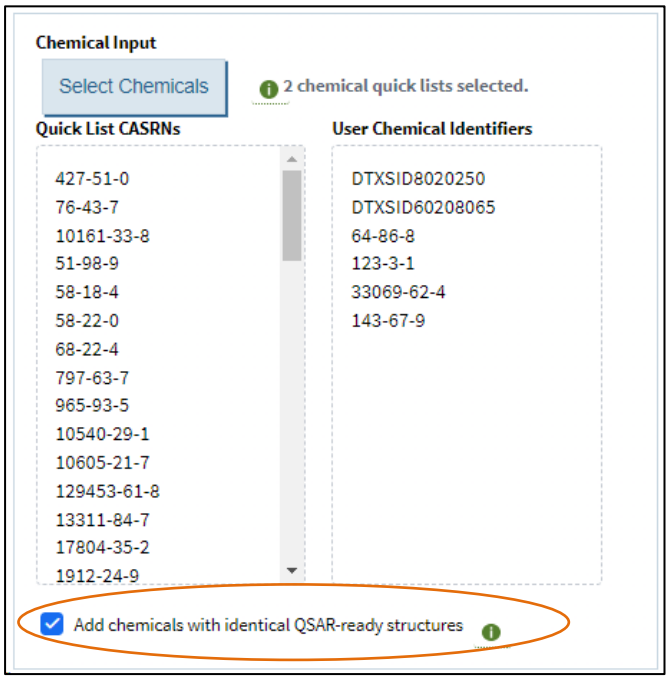

Figure 3. Add in chemicals with the same QSAR structure.

Data Selection

You can select data sets that are organized in categories around major regulatory endpoints, with additional categories allowing you to select data from in vitro curated high-throughput screening (cHTS) assays, chemical property data, and exposure predictions.

To select data sets for your query, click on the "Select Data Sets" button in the Select Data Sets field on the right. This will open a dialog box (**Figure 4**) with a series of category tabs across the top, representing major regulatory endpoints (for example "Acute Lethality" and "Sensitization"). There are also tabs for chemical parameters (including physicochemical parameters), exposure predictions, and curated high-throughput screening (cHTS) data (discussed in **Appendix 1**).

Figure 4. ICE Search data set categories.

Within each category, data sets are organized in a parent-child relationship. Expanding the parent term using the arrowheads will reveal additional child terms (**Figure 5**). The terms at the lowest level are for specific categories. Annotations in a column to the right of the category name indicate if it is in vivo, in vitro, in silico, integrated approach or measured. Selecting a parent term will automatically select all categories under that term (**Figure 5**).

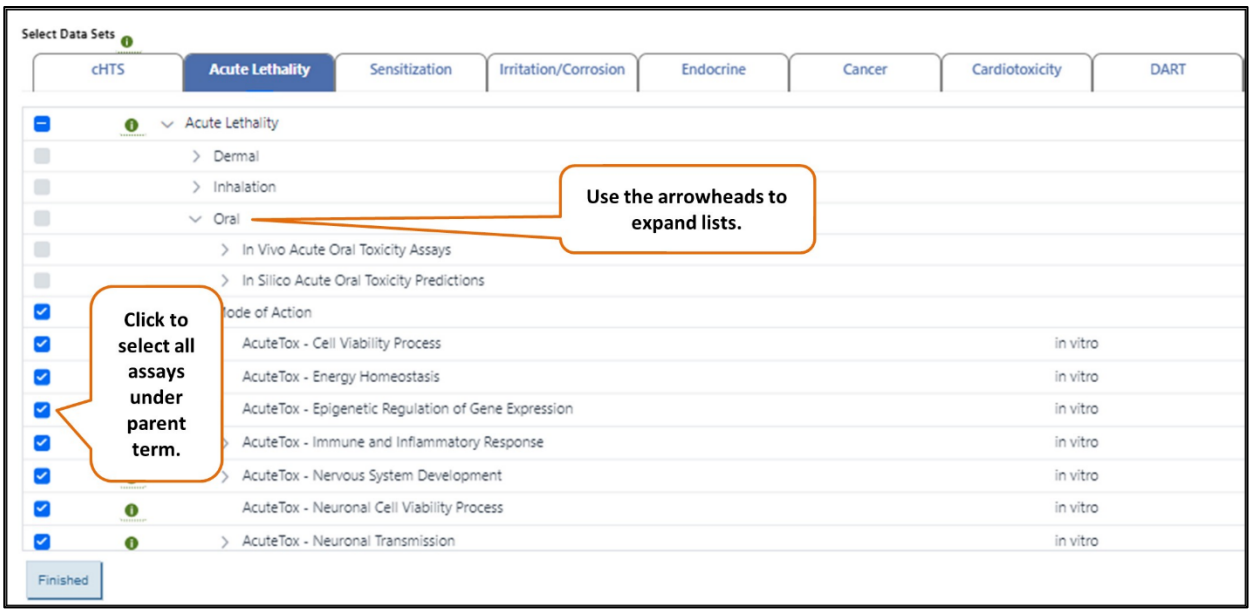

Figure 5. Select assays from a parent term data set category.

To add data from more than one category (**Figure 6**) click on the tab to select the category, then continue to select checkboxes to select additional categories. When you are done making your selections, click "Finished."

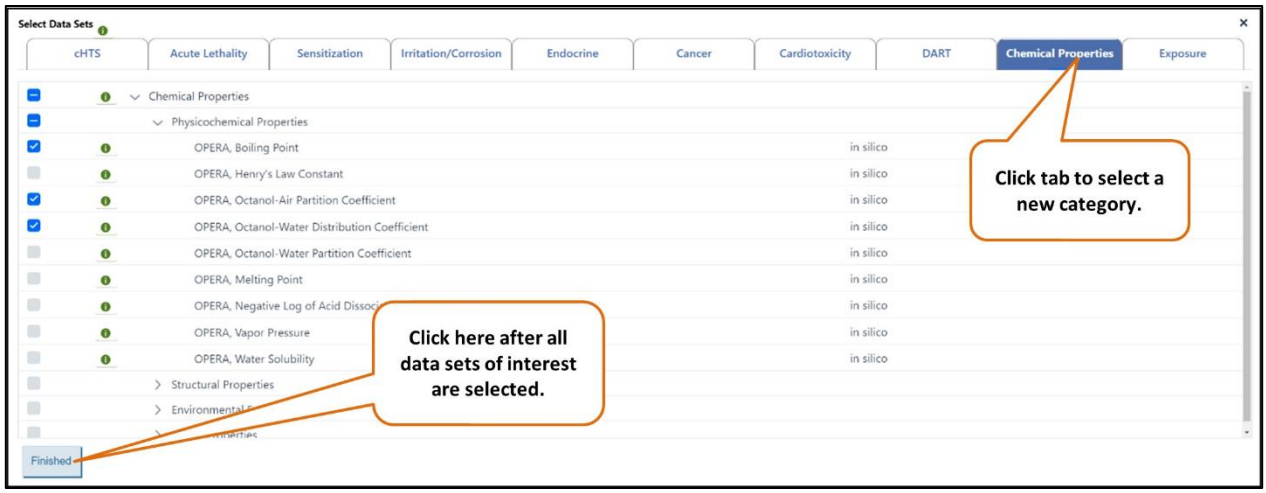

Figure 6. Select data sets from an additional category.

The selected categories will appear in the Data Set box (**Figure 7**). To add more data sets, you will need to click on the "Select Data Sets" button again. To remove categories from the query, deselect the checkbox to the left of the category name. To clear the query, select the "Reset" button.

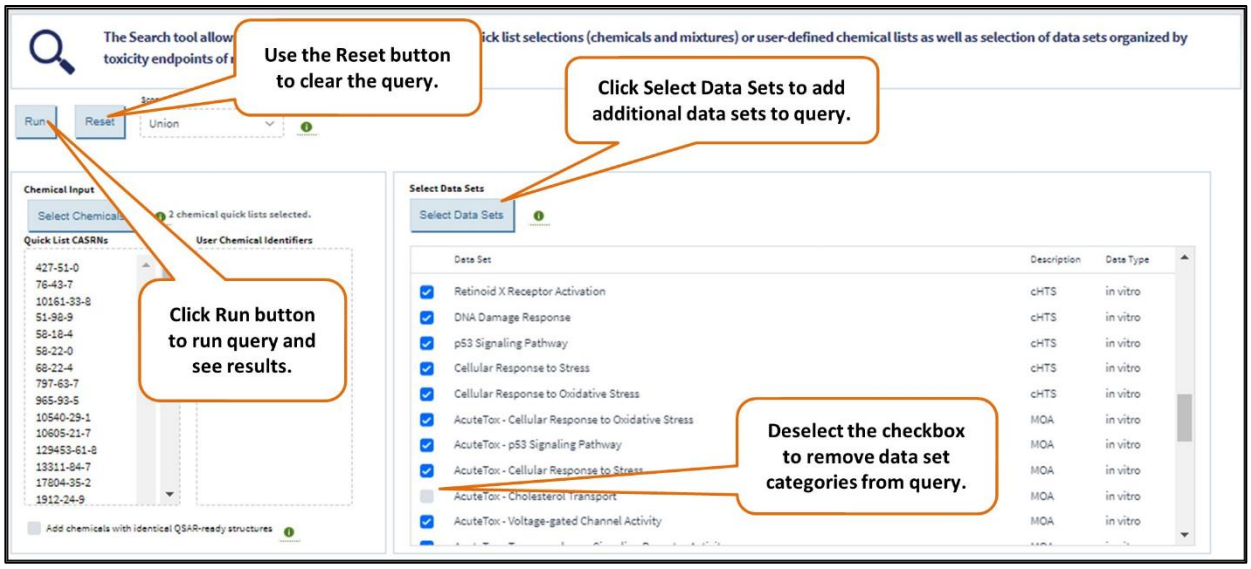

Figure 7. List of selected chemicals and data sets.

Selecting Data Sets Based on Modes of Action

Some toxicity endpoints (for example "Acute Lethality") include a Mode of Action term. These are curated groupings of cHTS assays that have been annotated to a mode of action based on the mechanistic target of the assay. Selecting a mode of action term will automatically add the individual in vitro assays to the query, but only the mode of action name will appear in the input field. In the example shown in **Figure 7**, the mode of action "AcuteTox-Cellular Response to Oxidative Stress" is included in the query; the mode of action "AcuteTox-Cholesterol Transport" was initially included but has been deselected and will not be included in the query.

cHTS Data Selection

ICE cHTS data include a curated set of ToxCast and Tox21 assays that have been mapped to mechanistic targets such as "Cellular Process" or "Cellular Stress Response." The cHTS data are organized based on these targets and the relevant term relationships from the Open Biological and Biomedical Ontology (OBO) Foundry. Selecting a mechanistic target within the cHTS category will populate the query with all cHTS assays relevant to that target. Mechanistic target labels, but not the individual assays, will appear in the Data Sets input field. The mechanistic target labels may be deselected like other types of data sets. See **Appendix 1** for more information about annotation of cHTS assays to mechanistic targets.

Other Search Options

The Search tool gives you two options to define the scope of your search (**Figure 8**). The default option, Union, returns results for the input chemicals on any data sets specified in the search query. The more restrictive option, Intersection, returns data set results only for chemicals that were tested in all the selected data sets for the search query.

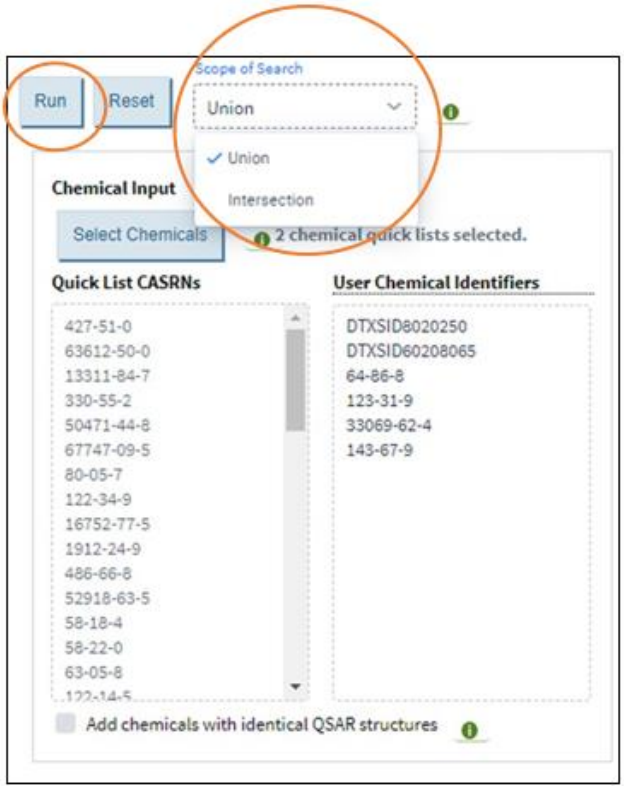

Figure 8. Choose "Union" or "Intersection" to expand or limit the scope of your search. Once completed click "Run".

Run Search

Once you have selected chemicals, data sets, and other options, click the "Run" button (**Figure 8**) to run your query. To reset inputs, click on "Reset".

ICE Search is limited to returning 10,000 substances. If entire data sets are desired, please contact NICEATM ,go to the Data Setspage,, or use the ICE REST API.

Viewing Search Results

The window will switch to Results view (**Figure 9**) after the query is run. Use the menu at the top left to return to Input view to review or change your query parameters and rerun your query.

At the top of the Results view are three clickable headings that allow you to view your chemical list inputs, data set query inputs, and identifiers not returned by the query.

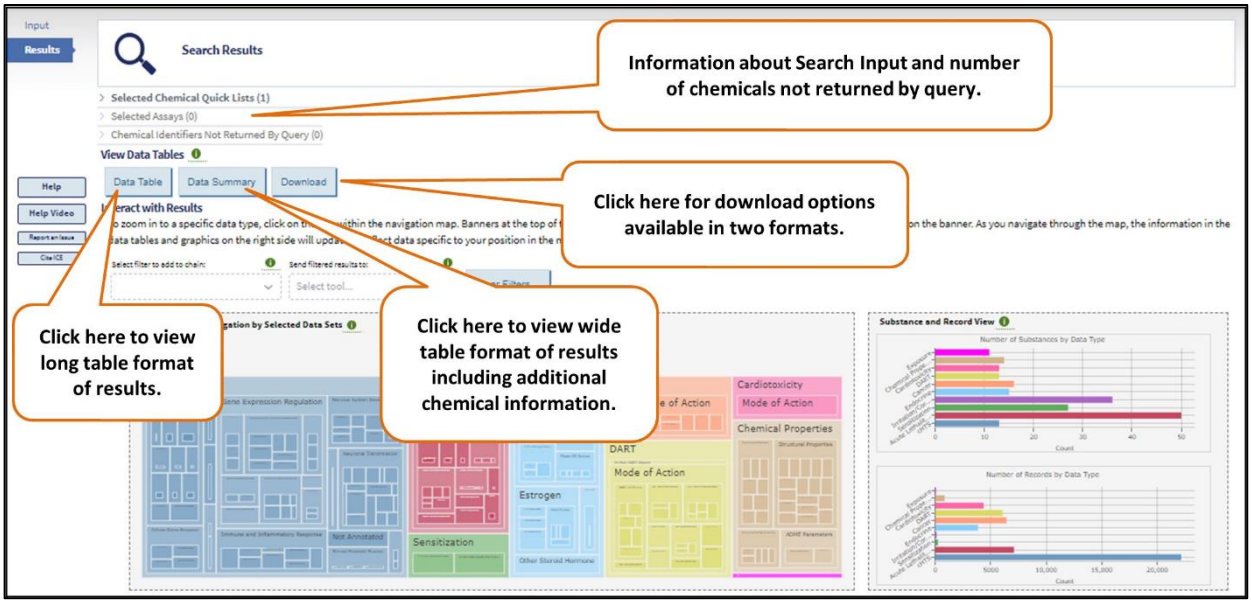

Figure 9. ICE Search data tables and download options.

Summary Data Tables

Along the top of the Search Results, there are three buttons that allow you to view or download data tables with the results from your query (**Figure 9**). Clicking the "Data Table" button displays a long view of the table with individual record data for each chemical-endpoint pair. Clicking the "Data Summary" button displays a wide view of the table that summarizes results for each chemical-endpoint pair. Clicking the "Download" button displays options for downloading the long and wide view tables.

In both the long and wide view tables, you have two options to view more information about an individual chemical.

- Click on the 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 the chemical's DTXSID to be directed to the EPA's CompTox Chemicals Dashboard entry for that chemical, which provides the chemical structure and other physicochemical and experimental properties.

Data Table (Long View)

Each row in the Long View data table displays data for each substance-endpoint record (**Figure 10**). Data provided include substance information such as substance name, substance type (chemical or mixture), CASRN, DTXSID, QSAR-Ready ID and data set information including data set name, endpoint in the data set, response, unit (for which response is specific), species, receptor species, route, sex, strain, life stage, tissue, lesion, location, assay source, gene, Gene Entrez ID, and in vitro assay source. References, reference URL and PubMed ID are also included. If "Add chemicals with identical QSAR-ready structures" was selected in input, an additional field representing "Is related chemical? " also appears.

To exit the long view, click the "x" in the top right corner or "Close" in the bottom right corner of the window.

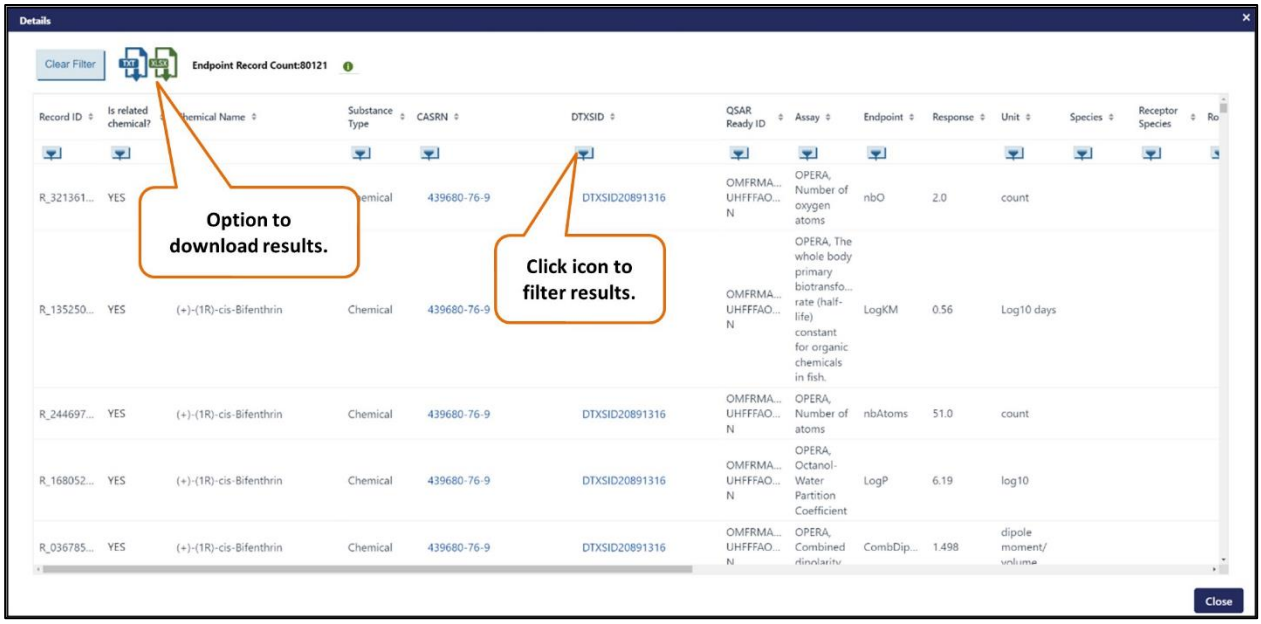

Figure 10. Data Table (Long View) for selected substances and data sets.

Data Summary (Wide View)

Each row in the Wide View data table displays data for each substance, with results summarized for substance-endpoint pairs. The first column of the data summary table displays a "View Details" button for each substance that will show detailed information about a specific substance. If "Add chemicals with identical QSAR-ready structures" was selected in input, a field representing "QSAR Match" will appear. Data provided in the Wide View table include substance name, substance type (chemical or mixture), CASRN, DTXSID, QSAR-Ready ID and output assay category names/endpoint fields (**Figure 11**). To exit the wide view, click the "x" in the top right corner or "Close" in the bottom right corner of the window.

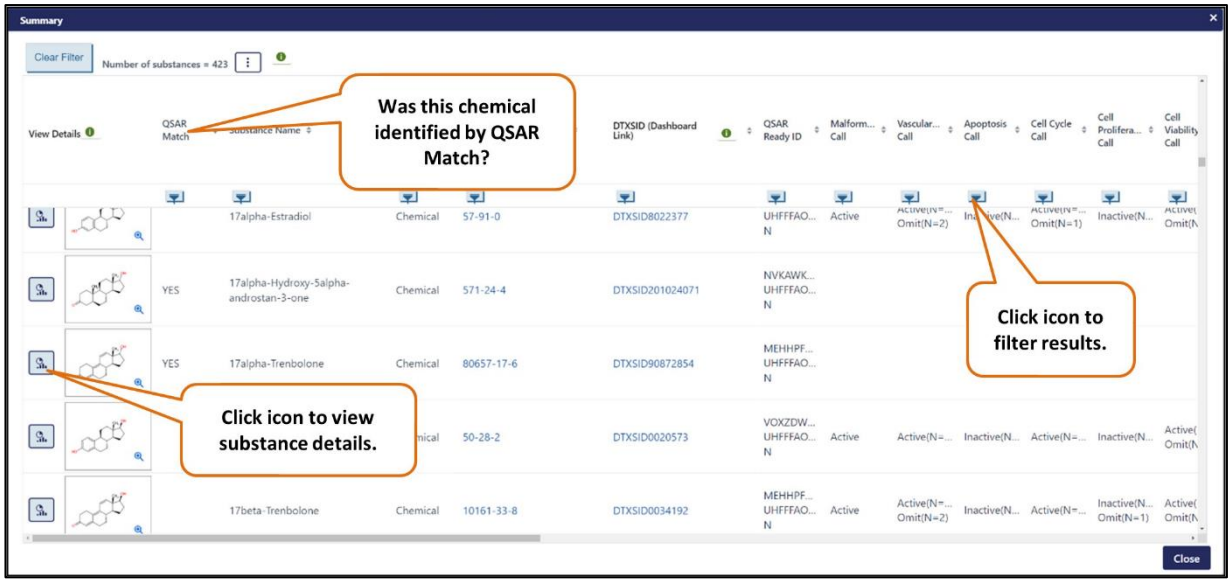

Figure 11. Data Summary (Wide View) for selected substances and data sets.

View Substance Details

The first column of the data summary table displays a "View Details" button for each substance. Click on this to view detailed information on a specific chemical or mixture. This view contains two tabs, "Substance Details" (or "Mixture Details") and Curve Surfer.

For a single chemical, the "Substance Details" tab (**Figure 12**) displays the chemical structure and physicochemical properties in the left-hand side of the window. The rest of the window displays a plot of bioactivity results. If cHTS assays are selected, results are grouped by mechanistic target or mode of action. The bioactivity is presented in two plots.

- The pie chart, which appears below the legend, presents the combined assay calls for the chemical.
- The stacked bar graph to the right of the legend displays assay call count. You can change the format of this graph from stacked bar to pie chart and display assay call count as percentages by selecting the different options under "Plot Type". Clicking any bar graph with an active call will open a separate window with AC50 box-and-whisker plots for that endpoint. To view the response per assay, click “view by assay.”

Bioactivity calls for all assays can be "Active" or "Inactive". Bioactivity calls for cHTS assays may also be flagged as "QC-omit" or "Flag-omit" during data curation. If a chemical was not tested in an assay, the result is labeled "Not tested" and hidden from the graph by default. For more information about the cHTS curation pipeline, see the cHTS data sets page.

Click on the graph “Legend” to remove or add data from both the pie chart and the bar graph. You can also select which assay types are included in the graph view by clicking the "Select Assay Type(s)" dropdown above the legend.

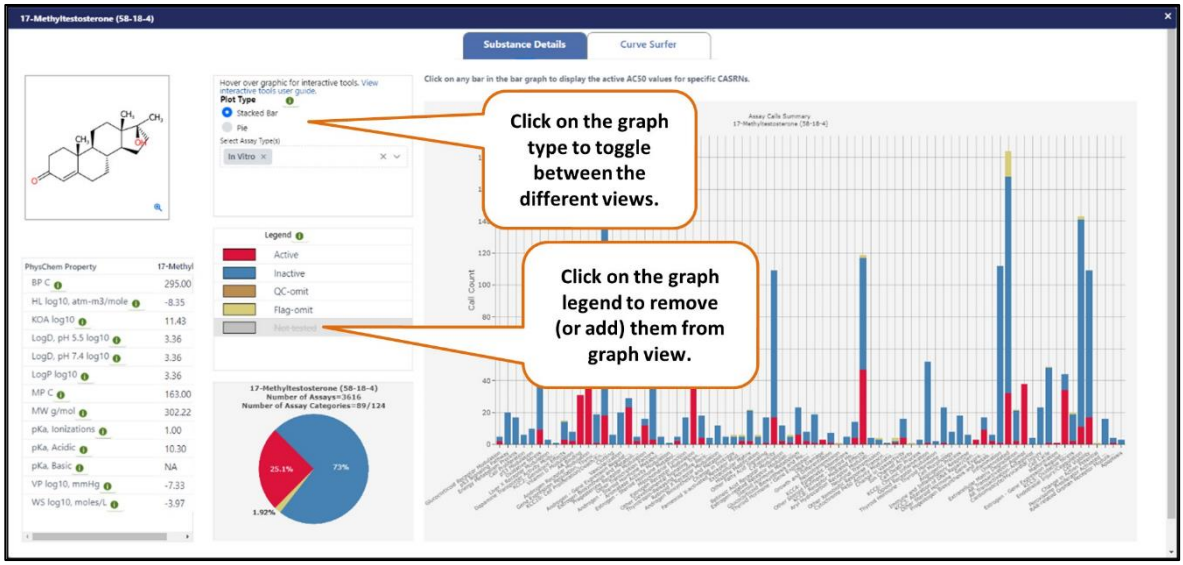

Figure 12. Substance Details view for a single chemical.

For a mixture (**Figure 13**), the Mixture Details tab displays information on the percent active ingredients both as a table and a pie chart in the top left. Click on the table rows to add or remove specified active ingredient slices from the pie chart. Note that once a slice is added or removed the percentages on the

pie chart changes accordingly. If only one active ingredient is selected or present the pie chart will read "100%".

Below the list and pie chart, box-and-whisker plots show AC50 (concentration that causes a -half-maximal response) and LD50 (test chemical dose that would be expected to cause death in 50 percent of animals in traditional tests for acute oral or dermal systemic toxicity) values for each active ingredient, if available in ICE. Use the left and right arrows to view both plots. Hover over points on the plot to view the assay names and values for each point.

The right side of the window shows the chemical structure and physicochemical properties for each active ingredient. You may need to use the scroll bar along the bottom of the window to view all the data.

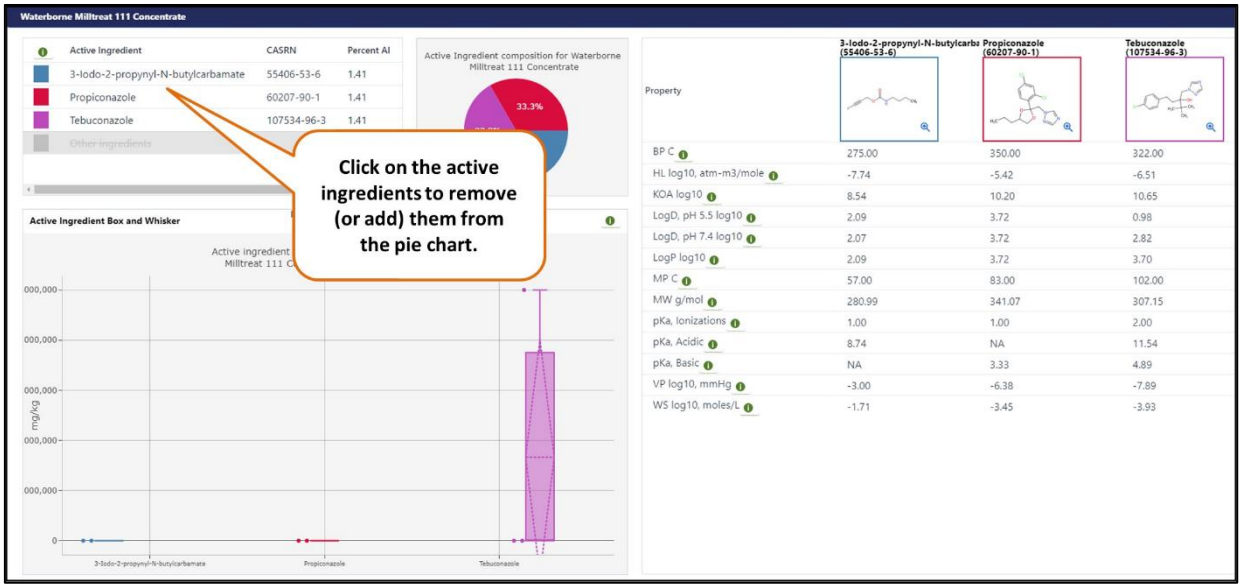

Figure 13. Mixtures Details view.

In either the single chemical or mixture Details view, the Curve Surfer tab (**Figure 14**) allows you to view and interact with concentration–response curves from cHTS data. You can select the dropdowns to filter the view or reorder the graphs. For complete details on how to use all Curve Surfer features, please refer the Curve Surfer User Guide. To exit the "Details" view, click the "x" in the top right corner of the window.

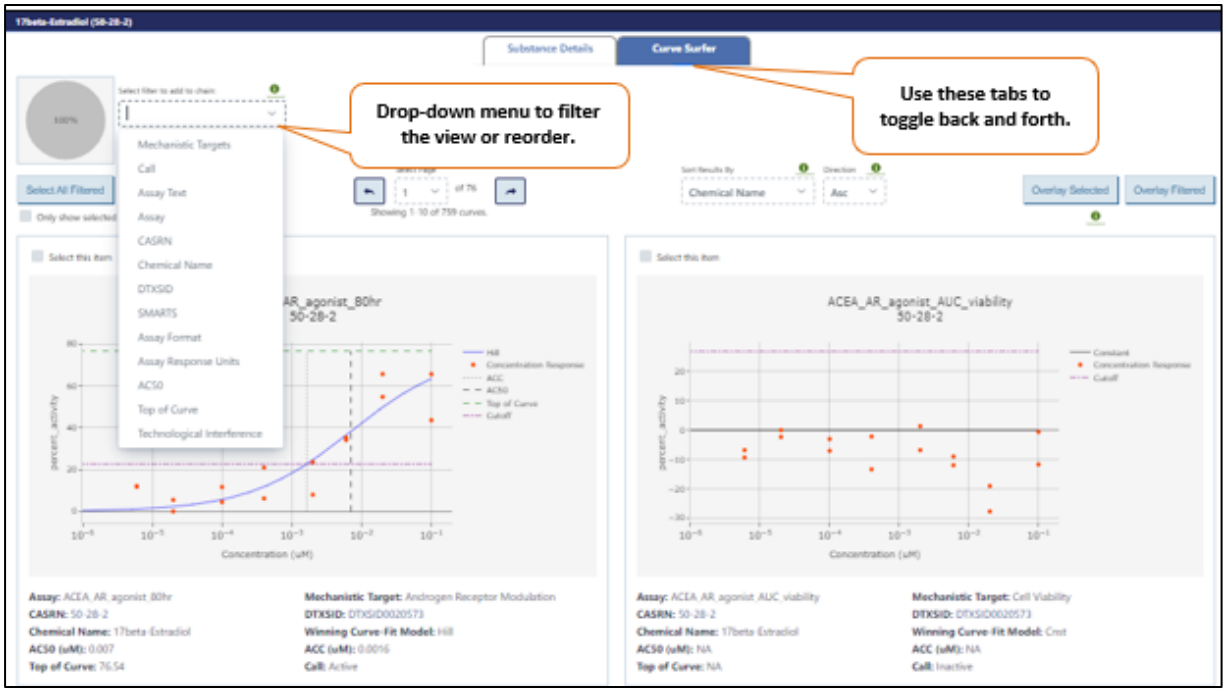

Figure 14. ICE Curve Surfer view for a single chemical or mixture.

Explore the Data Summary Contents

After the "View Details" button, the chemical structure for the chemical in that row is shown. Click on the magnifying glass in the lower right corner to view this in a larger window.

If the option "Add chemicals with identical QSAR structures" was selected during data input, a "QSAR Match" column will be present to the right of the "View Details" column in the data table (**Figure 11**). Entries in this column indicate if a chemical in the query was added due to having the same QSAR-ready structure as one in the input.

The next five columns contain identifier information for each chemical or mixture. To filter results on specific identifiers (**Figure 11**), click the "Filter" icon below the column names to open a dialog box, then select checkboxes to select a subset of your results. There is a text box at the top of the filter that will allow you to type in a selection. After you have made selections, click on the "Close" button. Click the "Clear Filter" button above the table to clear filters.

The columns following the identifiers display results from the selected data sets. If multiple data points exist for a substance–assay/endpoint pair, the median value is displayed. If an endpoint is categorical, a summary is provided. Use the scroll bars to the right and below the table to view the entire table. To exit the Summary view, click the "x" in the top right corner or "Close" in the bottom right corner of the window.

Download Results

You can download your results to your desktop. When you click "Download" there are three options to download your results depending on the assays queried (**Figure 15**).

- **Summary Data** provides information for each substance on a single row. If more than one datapoint is present for an endpoint, the number of data points, median, and range are provided. cHTS data are provided as group summaries.
- **Long Format Data** returns each unique chemical-assay combination as a single row. This format may be more useful for running additional analyses on Search results.

A third download option, **Wide Format Data**, is only provided for queries that include cHTS assays. This file is similar to Summary Data, with summary calls and statistics for AC50s provided for each active cHTS assay included in the query.

Each format is available for download as a tab-delimited or Excel file. Any filters applied to the display will also be applied to the download.

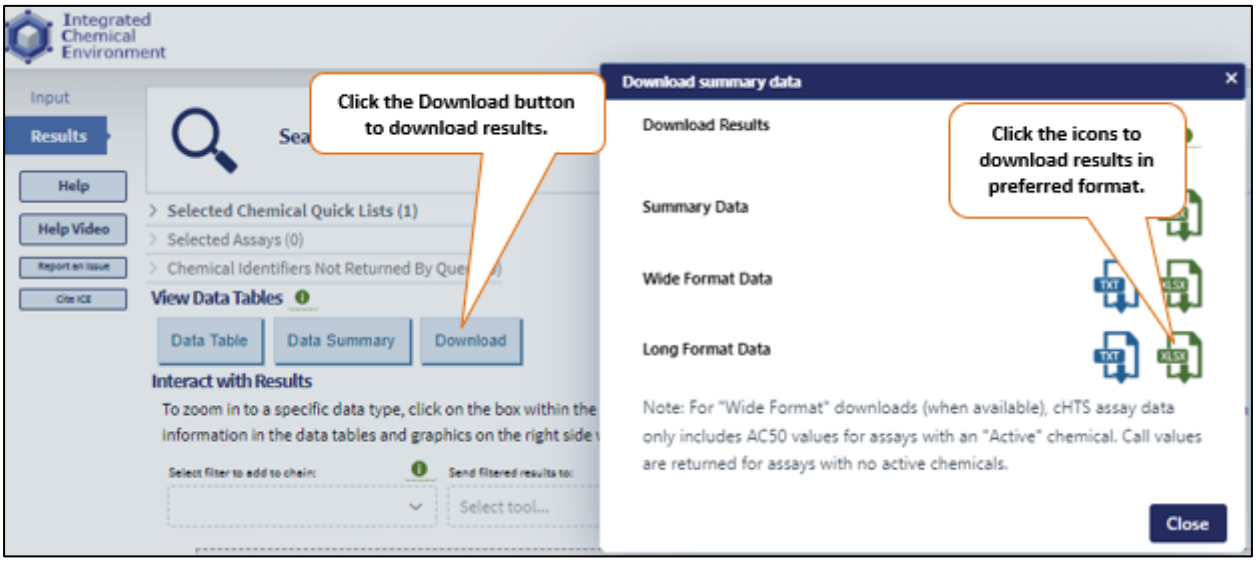

Figure 15. ICE download options for a search.

Interact with Results

At the bottom of the page, results are visually summarized with tables and graphics describing the data and endpoints available based on your chemical and data set selections (**Figure 16**).

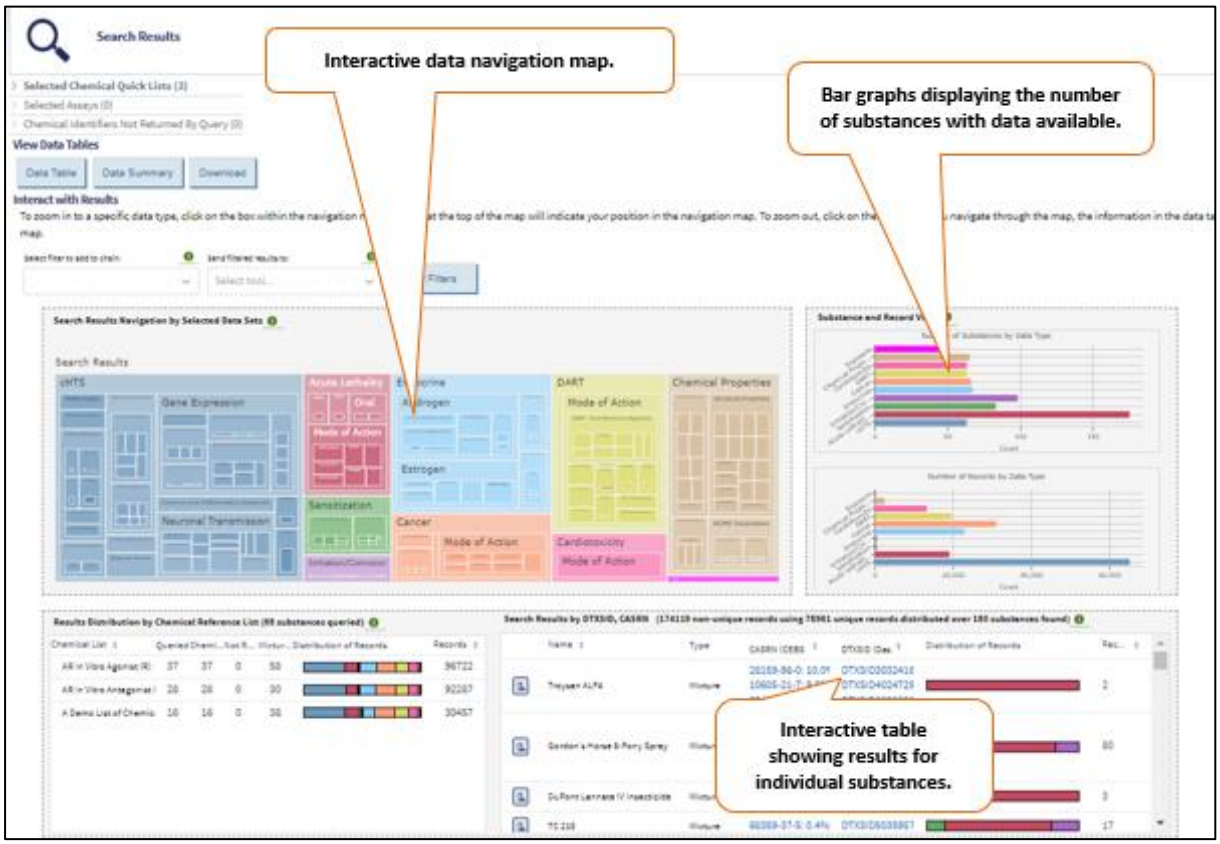

Figure 16. ICE Search Results overview.

Data Navigation Map

On the top left side of the data graph section, an interactive data navigation map shows the distribution of records returned across the data types selected. The nested boxes in the map represent subsets of the results according to data type hierarchy. Hovering over a box will display the number of records in the results that correspond to that data subset.

Click on boxes within the map to zoom in on a data type and view the specific endpoint data available for a selected data type subset (**Figure 17**). As you zoom into the map, your location within the map's hierarchy is displayed as sequential banners above the map. Click on the banners above the map to zoom back out to a higher level in the map. All panels in the data graph section will update to reflect only the subset of data you are zoomed in on. The bottom of the screen will populate with visualizations of data specific to that subset. Currently, filters applied through the navigation map do not affect the Data Table, Data Summary, or Download features above. However, this functionality will be made available in the future.".

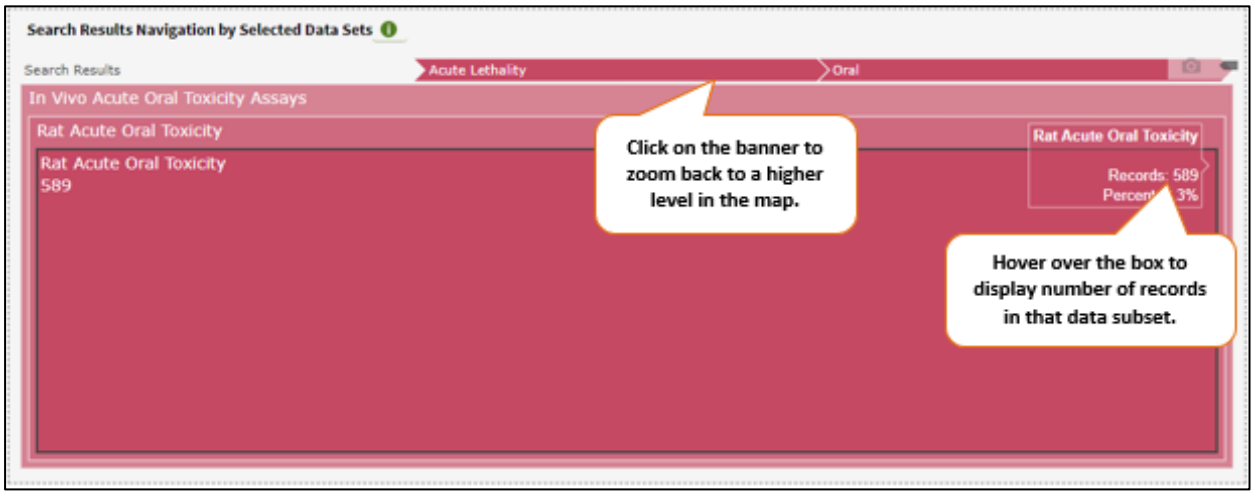

Figure 17. Interactive data navigation map.

Data Visualizations

Navigating through the data navigation map on the left side of the Query Summary view will populate the bottom of the screen with graphs. Graphs are grouped into individual cards that are specific to the selected data subset and data type (**Figure 18**). As you navigate through the data navigation map, the graphs will update to reflect your selection in the map.

At higher levels of the navigation map, data subsets with multiple assays and common binary or categorical endpoints will be displayed as bar charts. The bar charts display assay category counts for each substance-endpoint pair. (**Figure 18**). At lower levels of the navigation map, a card is created for each assay or non-assay endpoint in the selected data subset. For any data subsets that have binary, categorical, or quantitative endpoints, cards are created to display the endpoint distribution.

- The top of each card contains color bars for any binary or categorical endpoints. Each color bar visualizes the proportion of binary or categorical responses. Hovering over a section of the color bar will display the corresponding category counts.
- The bottom of each card contains density plots for each quantitative endpoint. Individual data points are overlaid on the density plot. Hovering over a point will display the chemical name, CASRN, and endpoint value.

Figure 18. Card view of search results for selected data sets.

Data subsets that are based on mechanistic target or mode of action terms are displayed as bar graphs. The bioactivity is presented in two plots, which are updated based on table filters (**Figure 19**).

- The pie chart below the legend presents the bioactivity for all selected assays combined.
- The stacked bar graph to the right of the legend displays assay call count for each selected cHTS assay. You can change the format of this graph from stacked bar to pie and display assay call count as percentages by selecting the different options under "Plot Type."

Click on the graph legend to remove or add data from the graph view. Click on the green information button for an explanation of the labels "QC-omit" and "Flag-omit. " You can also select which assay types are included in the graph view by clicking the "Select Assay Type(s) " dropdown above the legend.

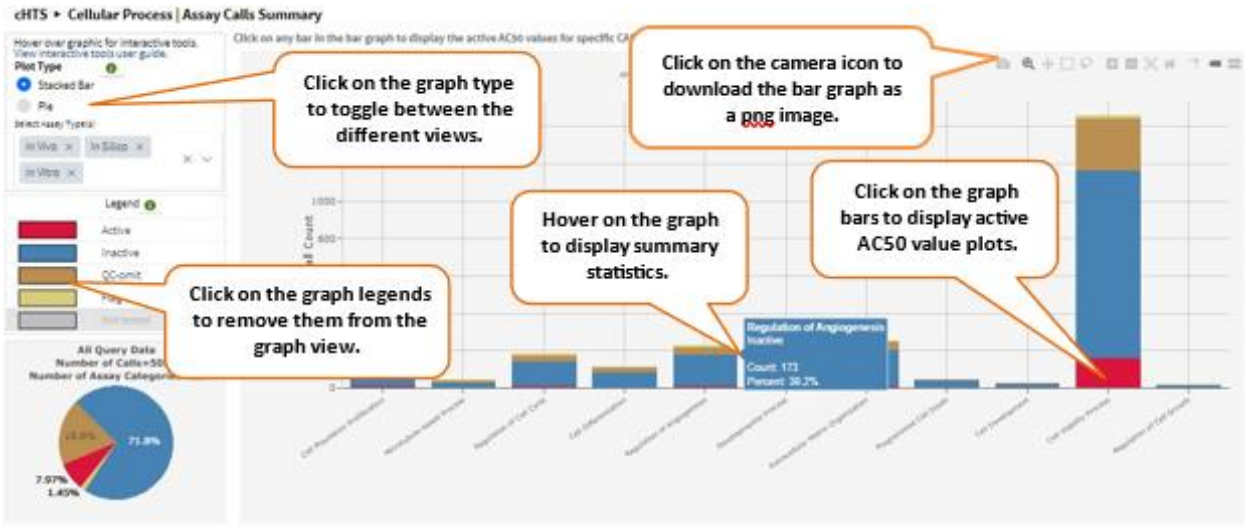

Figure 19. ICE Summary cHTS graphs for Search query.

Hover over the plot area to cause a menu to appear above the plot providing options for adjusting the view and exporting the plot. Hover over the data elements in the graph to display summary statistics of the data for each bar. To zoom in on specific data points, click and drag the cursor over a specific area on the graph, or use the toolbar in the top right of the plot area. Double-click on the plot to zoom back out. For more information about interactive graph visualization options, consult the Interactive Graphs User Guide.

Click on a bar within the bar graph to open a new window to display plots of active AC50 values for that assay type by CASRN. (The new window may take a few seconds to open.) You can interact with this graph in the same way as the main graph. Click on "View By Assay" button below the plot to viewactive AC50 values for individual assays within that assay type. Interactive density plots and bar graphs are downloadable as png images by selecting the camera icon in the upper right menu within each graph (**Figure 20**).

Query Summaries

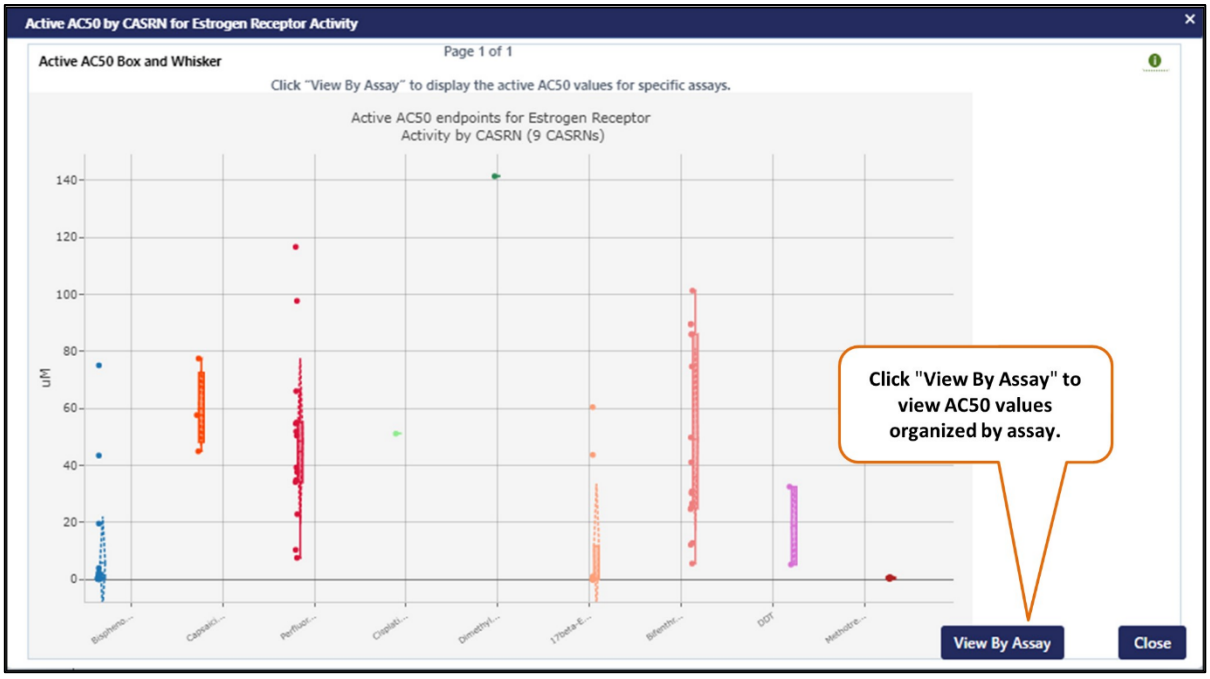

Figure 20. Active AC50 values organized by CASRN.

On the right side of the data navigation map, there are two bar graphs (**Figure 21**). The upper bar graph displays the number of substances with data available for a given data type. The lower bar graph displays the number of records available for a given data type.

Below the data navigation map and bar graphs, two tables are displayed (**Figure 21**). The table on the left provides a summary of the results returned for each chemical list. A note above the table states the total number of chemicals included in your query.

The table on the right shows the individual substances from the query that have data available for your data set selections. The chemical name, CASRN, and DTXSID are provided. The column "Type" indicates whether the substance is a chemical or a mixture. Clicking on the icon to the left of the substance name will display detailed information about that chemical or mixture.

In both tables, the last column contains colored bars that show the distribution of data type across the records available for the corresponding chemical quick list or individual substance. Hovering over a section of a colored bar will display the number of records and percent of data returned with the given data type for the corresponding chemical list or individual substance. You may need to use the scroll bars below and on the right side of each table to view the entire table. You can also sort the rows by clicking on the table headings or click and drag the table headings to adjust column widths.

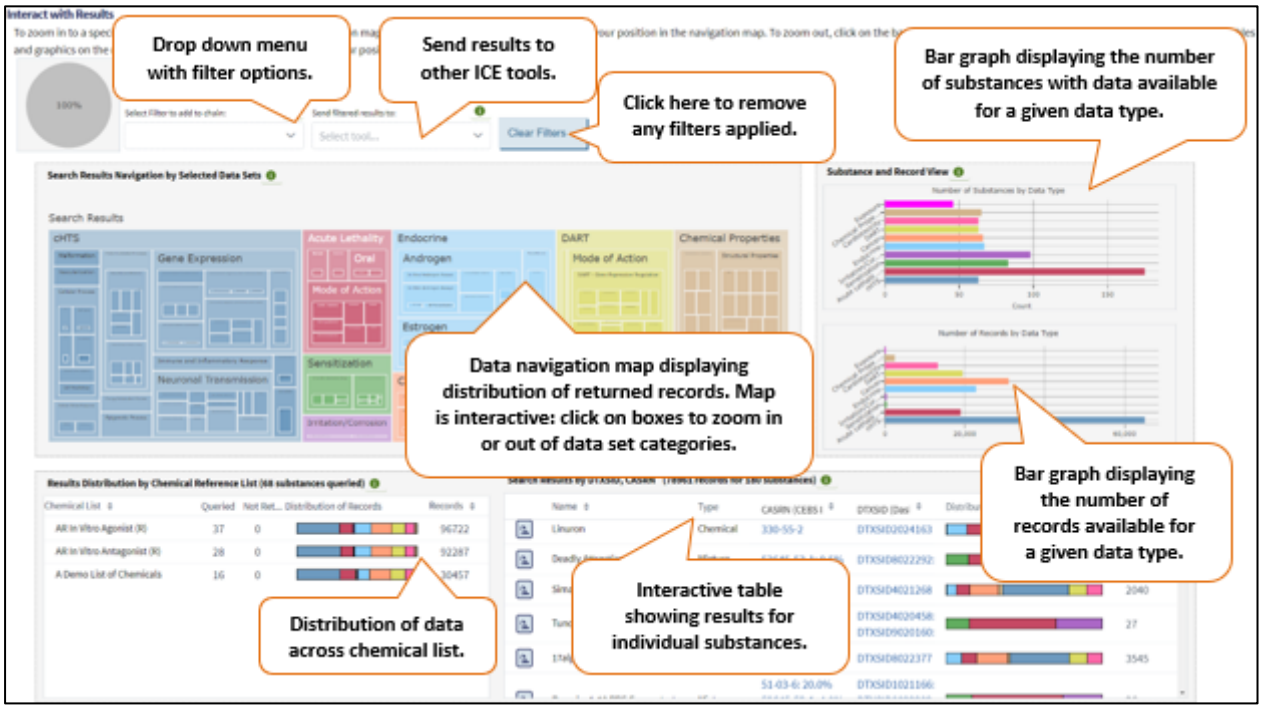

Figure 21. ICE Search interacting with results through navigation map, query summaries and Search results distribution.

Filtering Results

Click the "Select filter to add to chain" dropdown list (**Figure 22**) above the navigation map to choose different filtering categories.

Select a filtering category to open a dialog box allowing you to select criteria for that category. When you select your criteria and click "Apply Filter", a colored box will appear describing the category and stating the number of records that meet the chosen criteria.

You can add additional filtering criteria for which additional boxes will appear.

You can click and drag the boxes to reorder them or click the "x" in the top right corner to remove a filter. Additionally, you can edit the filter by clicking the symbol in the bottom right corner of each selected filter box.

A pie chart to the left of the dropdown shows the number of records meeting the criteria in each layer of filtering.

Click the "Clear Filters" button to clear all filters.

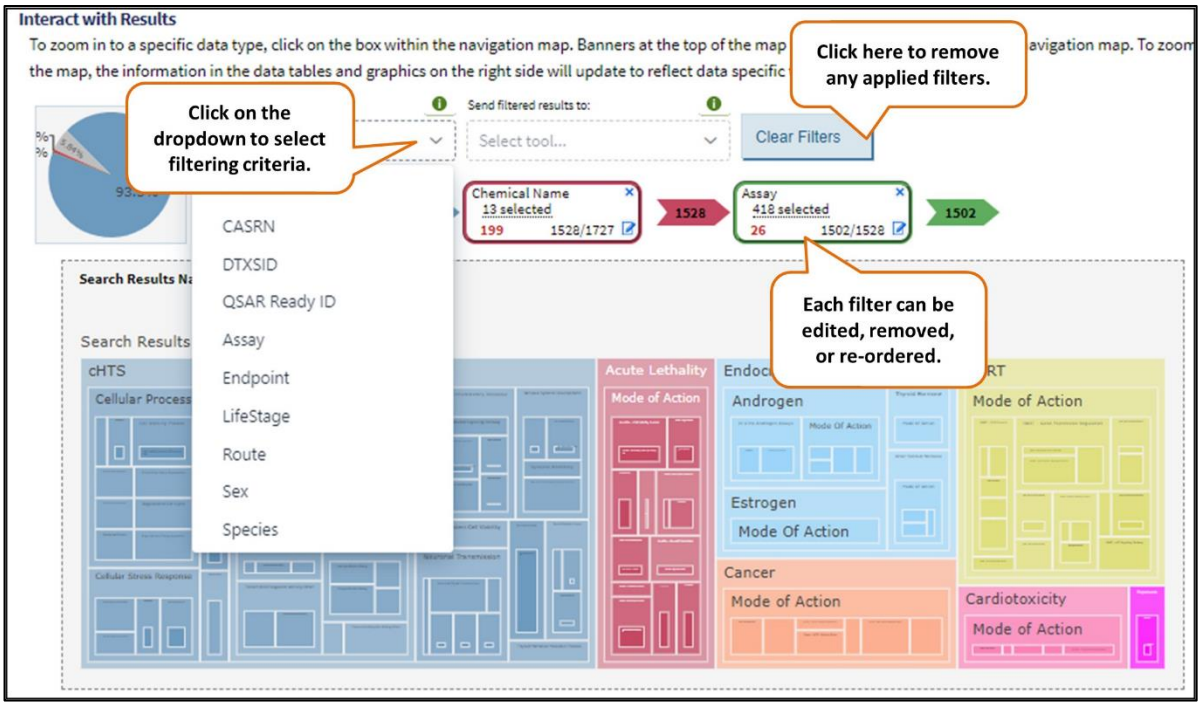

Figure 22. ICE Search filtering results.

Sending Results to Other ICE Tools to Run Additional Queries

Click the "Send filtered results to" dropdown list (**Figure 23**) next to the "Select Filter to add to chain" button to send Search parameters to other ICE tools. Filters and individual selections applied to results will define what is sent to other tools.For details on the use and outputs of these tools, refer to their User Guides.

- Click "Chemical Quest" to send chemicals to the Chemical Quest tool to query ICE for chemicals that are structurally similar to these chemicals.
- Click "Curve Surfer" to send chemicals and data set endpoints to the Curve Surfer tool.This tool will display activity curves for all available cHTS data in ICE.
- Click "PBPK" to send chemicals to the Physiologically Based Pharmacokinetics (PBPK) tool. This tool generates predictions of tissue-specific chemical concentration profiles following a dosing event.
- Click "IVIVE" to send chemicals and cHTS assays to the In Vitro to In Vivo Extrapolation (IVIVE) tool. This tool estimates the daily equivalent administered dose (EAD) 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 send chemicals to the Chemical Characterization tool. This tool allows you to view physicochemical properties, absorption, distribution, metabolism, and excretion (ADME) properties, and chemical use categories of a set of chemicals. You can also copy CASRNs, DTXSIDs, SMILES strings, or QSAR-ready SMILES strings to the clipboard.

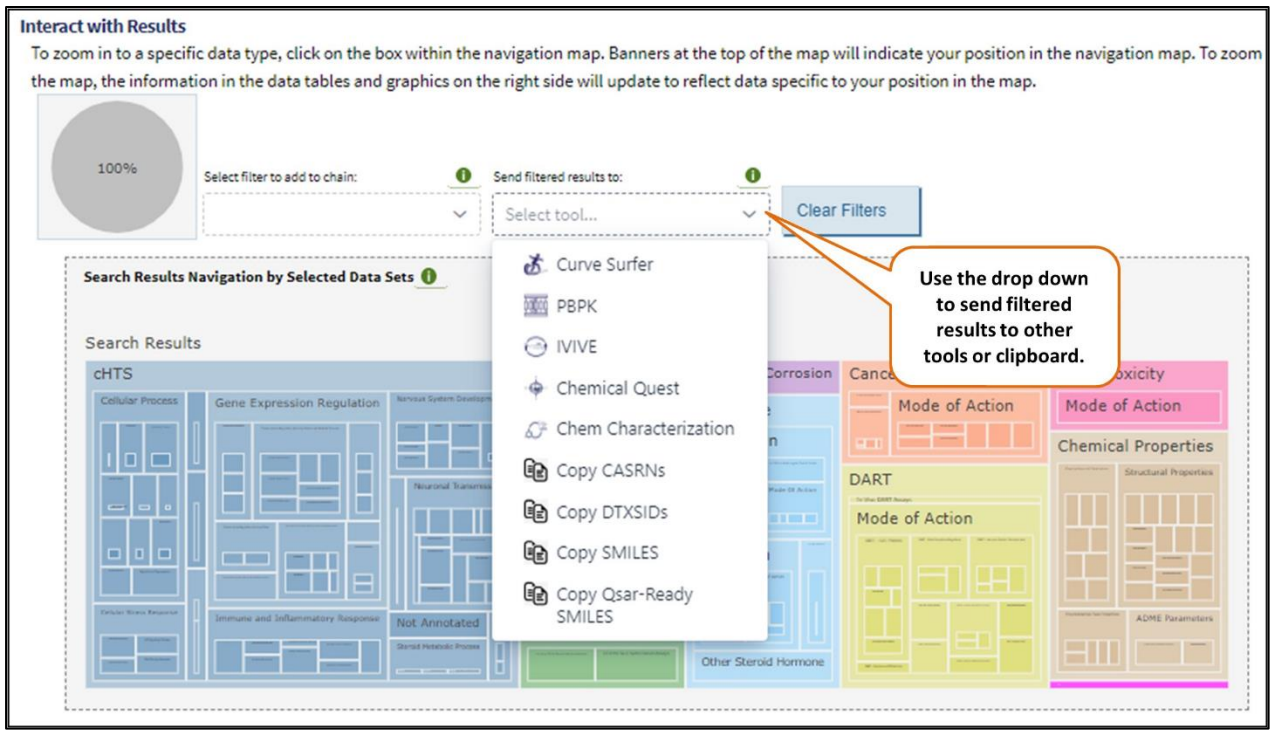

Figure 23. Send filtered results to other ICE tools.

Query ICE Using the REST API

You can use the ICE REST API to obtain curated in vivo, in vitro, and in silico toxicity data, chemical properties data, and exposure predictions from ICE without using the visual interface.

The ICE REST API can be accessed at https://ice.ntp.niehs.nih.gov/api/v1/search. Information about how to use the ICE REST API is available on ICE REST API User Guide page.

Citing ICE

You can easily gather ICE citation information through the “Cite ICE” button on the left panel. A new window will appear with citation information and additional ICE references.

Appendix 1: ICE cHTS Data

cHTS data in ICE were derived from bioactivity data from the U.S. government's interagency Tox21 collaboration including EPA's ToxCast program. These data were generated using quantitative high-throughput screening assays that have been developed and optimized in Tox21 and analyzed using EPA’s tcpl package. For inclusion in the ICE cHTS data, these data go through an additional curation, described briefly below and in detail in the ICE cHTS Data Sets page.

cHTS data in ICE are annotated to mechanistic targets that facilitate interpretation with regards to toxicological outcomes of regulatory interest. Annotation to mechanistic targets considers:

- Annotation information provided in the invitrodb v3.5 annotation files. Examples of fields used include "intended_target_family" and "biological_process_target. "

- Additional information on the assay or platform available in publications or through the Tox21and ToxCast programs.
- Terminology used in the Open Biological and Biomedical Ontology (OBO) Foundry (referred to as "mechanistic targets" and "mode of action" in ICE).

Terms from the curated annotation and assay information are mapped to terms from the OBO Foundry to create connections to widely used and established terminology with controlled identifiers. The organized annotations incorporating ontologies were primarily obtained from the Gene Ontology (GO) knowledge base. This allows the annotations found in ICE to be accessed more broadly and the ICE data to be linked to other resources and terms, including toxicological endpoints of regulatory interest.

NICEATM continues the cHTS mapping process with expert review to annotate the mechanistic targets to terms derived from modes of action relevant to regulated toxicity endpoints as defined by published literature using terms like "regulation of vascularization" and "epigenetic process". These terms are curated to harmonize similar descriptors and ensure consistency and appropriateness of the annotation details.

Appendix 2: Abbreviations

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

AC50: concentration that causes a half-maximal response

ACC: activity concentration at cutoff

ADME: absorption, distribution, metabolism, and excretion

CASRN: Chemical Abstracts Service Registry Number

CEBS: Chemical Effects in Biological Systems (National Toxicology Program)

cHTS: curated high-throughput screening

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

DTXSID: DSSTox substance identifier

EPA: U.S. Environmental Protection Agency

GO: Gene Ontology knowledge base

ICE: Integrated Chemical Environment

InChIKeys: hashed International Chemicals Identifiers

IVIVE: in vitro to in vivo extrapolation

LD50: chemical dose expected to cause death in 50 percent of animals in traditional tests for acute oral

or dermal systemic toxicity

NICEATM: National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods

NTP: National Toxicology Program

OBO Foundry: Open Biological and Biomedical Ontology (OBO) Foundry

PBPK: Physiologically Based Pharmacokinetics

QSAR: quantitative structure-activity relationship

SMILES: simplified molecular-input line-entry system

Tox21: Toxicology in the 21st Century

ToxCast: Toxicity Forecaster (U.S. Environmental Protection Agency)