Tox21 Enricher
User's Manual

(Last Updated 12/30/2021)

http://hurlab.med.und.edu/Tox21Enricher

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I. Introduction to Tox21 Enricher

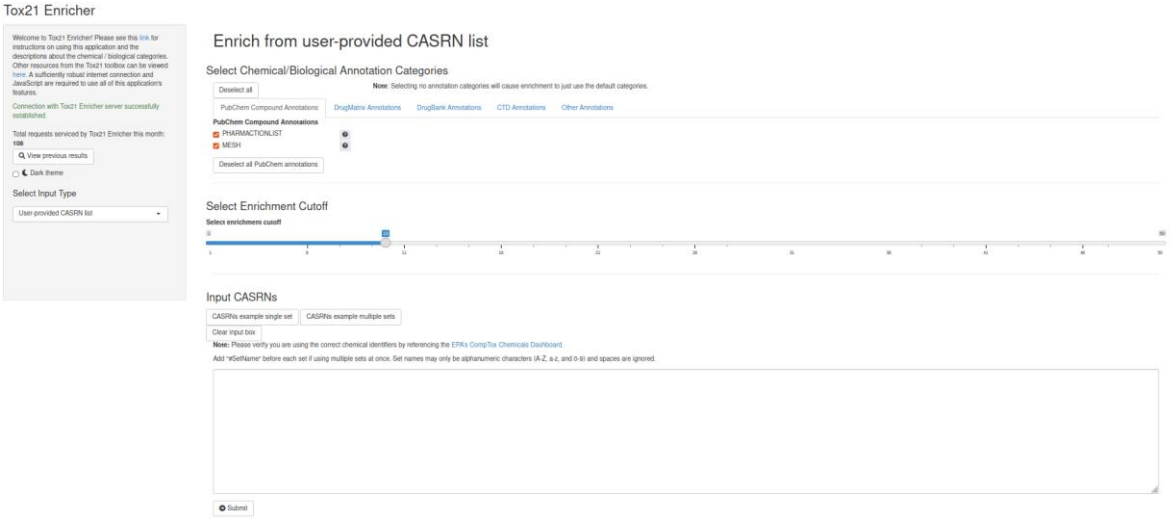
Humans are exposed to tens of thousands of chemicals that are used in daily life, some at levels that may pose a health risk. There is limited toxicological information for many of these chemicals, which makes risk assessment difficult or impossible. The United States Toxicology Testing in the 21st Century (Tox21) program was established to develop more efficient and human-relevant toxicity assessment methods. The Tox21 program is currently screening a set of over 10,000 chemicals, the Tox21 10K library, using quantitative high-throughput screening (qHTS) of assays that measure effects on toxicity pathways. To date, more than 70 assays have yielded >12 million concentration-response curves by Tox21 researchers. To efficiently apply these data for identifying potential hazardous compounds and for informing further toxicological testing, the United States National Toxicology Program (NTP) has developed several web applications (Tox21 Toolbox: **http://ntp.niehs.nih.gov/tbox/**), including tools for data visualization (Tox21 Curve Browser) and exploration (Tox21 Activity Profiler).

One critical usage of this dataset is to perform chemical-relational analysis based on the patterns of activity across the Tox21 assays and then to use nearest neighbor-based prediction to infer the toxicological properties of untested chemicals via their association with tested chemicals. One approach to inferring the specific properties is to perform chemical annotation enrichment of chemical neighborhoods.

Here, we present Tox21 Enricher, a web-based chemical annotation enrichment tool for Tox21 assay data built using the R Shiny framework. Tox21 Enricher identifies significantly over-represented chemical biological annotations among sets of chemicals (neighborhoods), which facilitates the identification of the toxicological properties and mechanisms in the chemical sets.

II. Landing Page

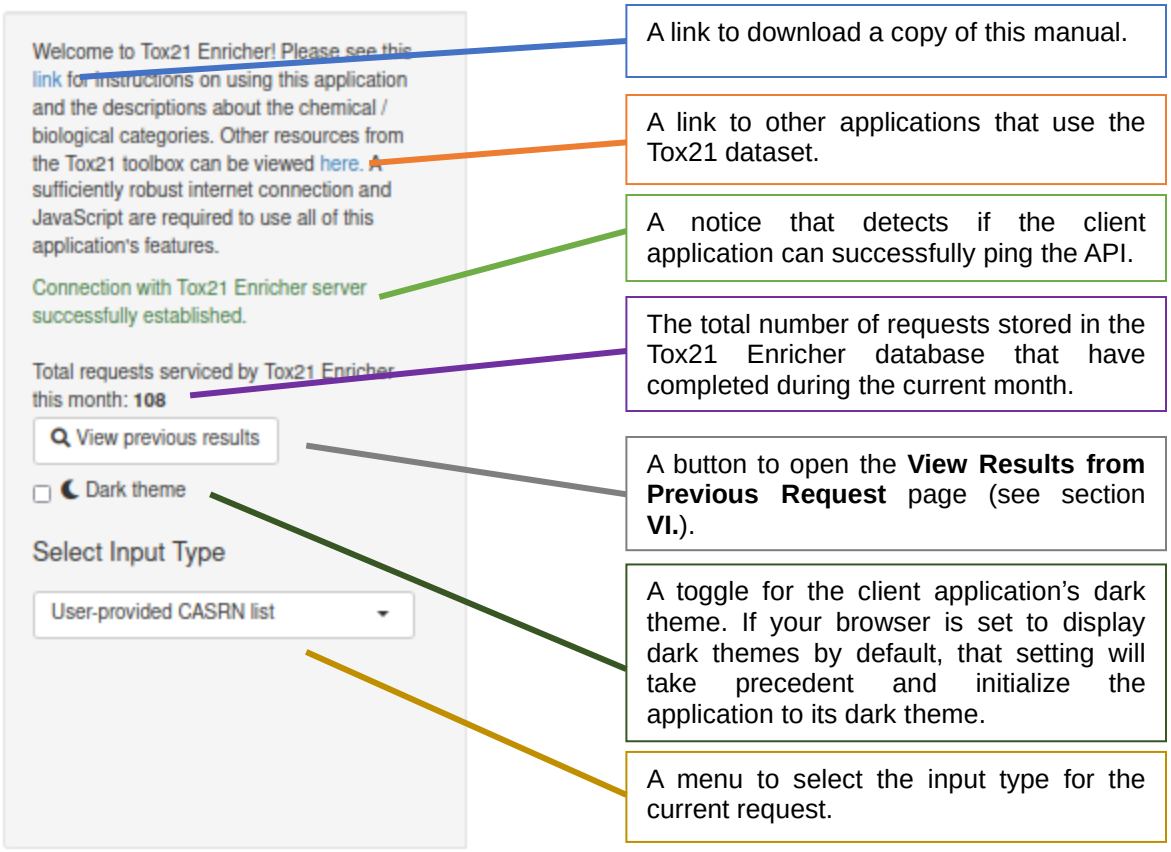
Upon first using Tox21 Enricher via an internet browser or directly through the client application, you will see the landing page.



The various utilities and options on the landing page will be discussed at length in this section.

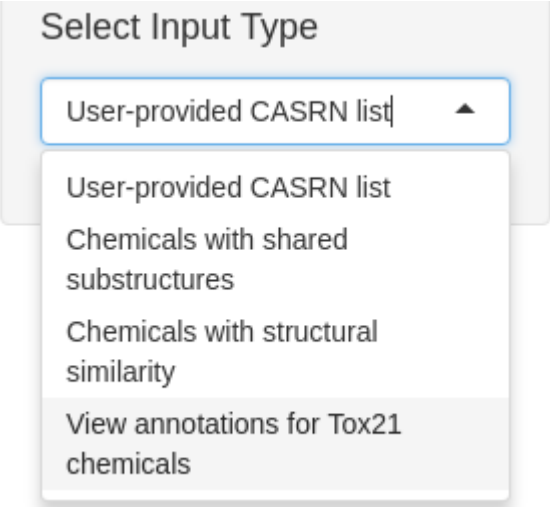
II.1. Sidebar

The sidebar of the application displays helpful information and various options and settings.



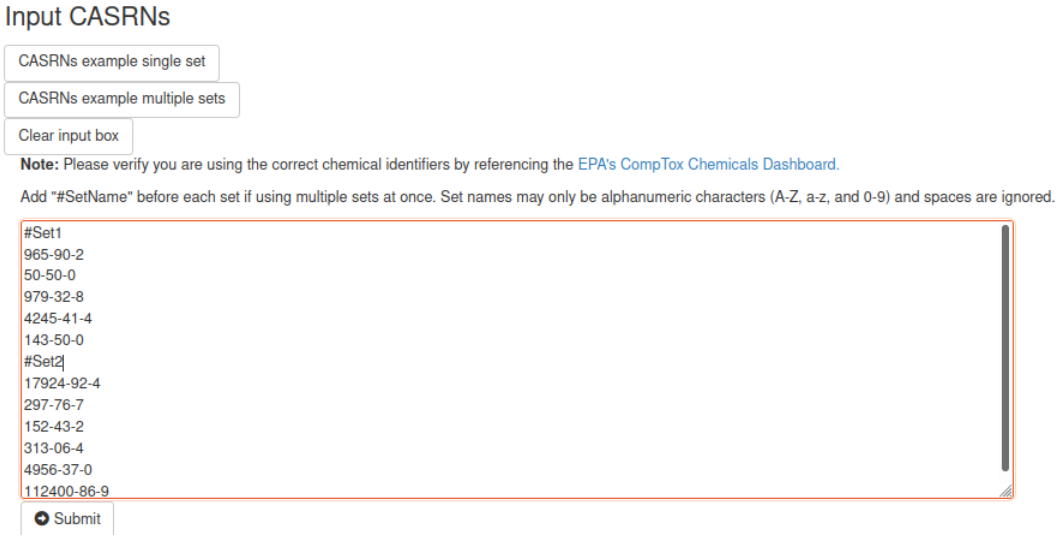
II.2. Selecting the Enrichment Mode and Input Type

The first step in using Tox21 Enricher is selecting the input type. There are three enrichment analysis modes: User-provided CASRN list, Chemicals with shared substructures, and Chemicals with structural similarity. A fourth mode, View annotations for Tox21 chemicals, does not perform enrichment but rather retrieves annotations from the Tox21 Enricher database that correspond to the inputted chemicals.



II.2.a. Enrich From User Provided CASRN List

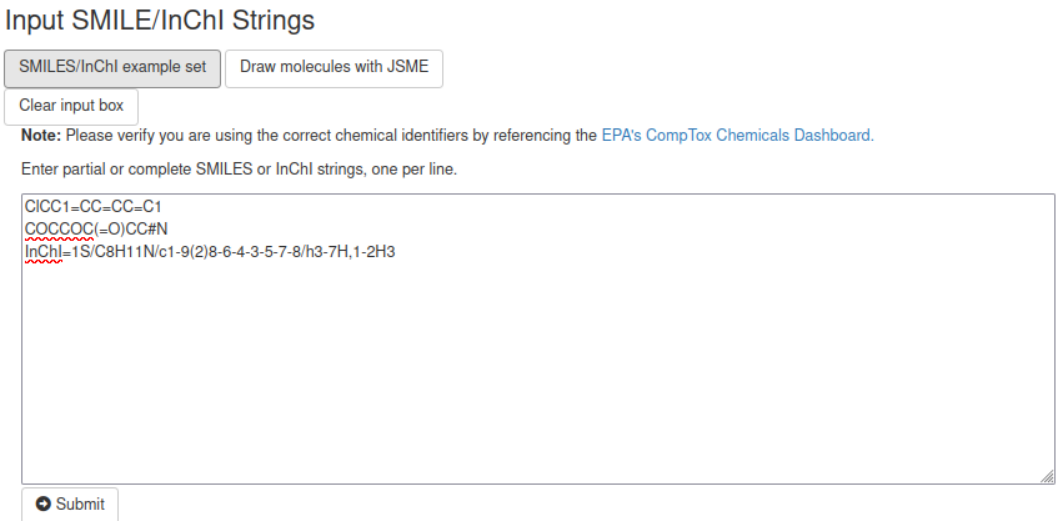
This enrichment analysis type accepts CASRN strings as input with one CASRN per line. Multiple sets may be independently enriched at the same time. To enrich multiple sets, separate lines of CASRN strings with **unique** set names of the form "#SetName" with a pound symbol (#) before the name. Only alphanumeric characters (A-Z, a-z and 0-9) may be used in set names. If you choose to provide names for input sets, **all** sets must be assigned a name. Spaces in set names or CASRN strings are ignored, and extra newline characters between lines are also ignored. If no set names are provided, all lines of the input box will be treated as one set and will be assigned the default name of "Set1."



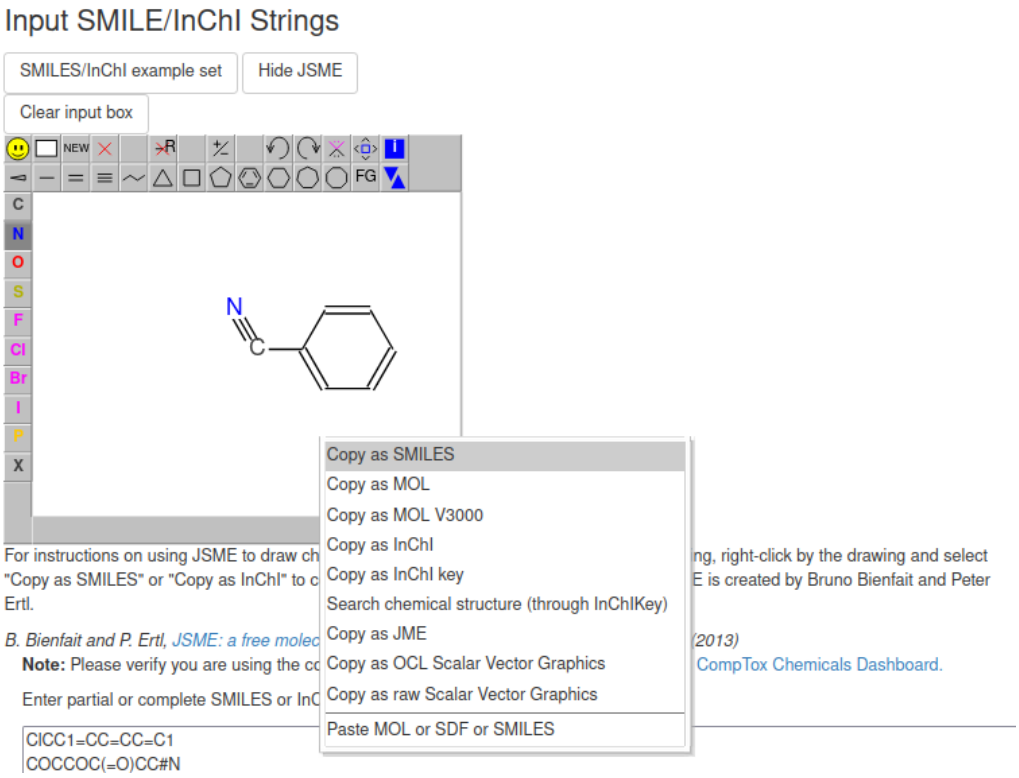
Before performing enrichment from a user provided CASRN list, please cross-reference your CASRN inputs with those in the EPA's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard) to ensure accuracy during the enrichment analysis. Clicking the **CASRNs example single set** button will fill the input box with one, unnamed set of CASRNs. Clicking the **CASRNs example multiple sets** button will fill the input box with three sets of CASRNs. Clicking the **Clear input box** button will reset the input box to a blank state.

II.2.b. Enrich From Chemicals With Shared Substructures

This enrichment analysis type accepts either SMILES or InChI strings (one per line). Each string is treated as its own data set and will be enriched independently of any other sets provided. SMILES and InChI strings may be mixed: you may perform enrichment with a SMILES string on one line and an InChI string on another. Clicking the **SMILES/InChI example set** button will fill the input box with three chemicals: two SMILES strings and one InChI string. Clicking the **Clear input box** button will reset the input box to a blank state.

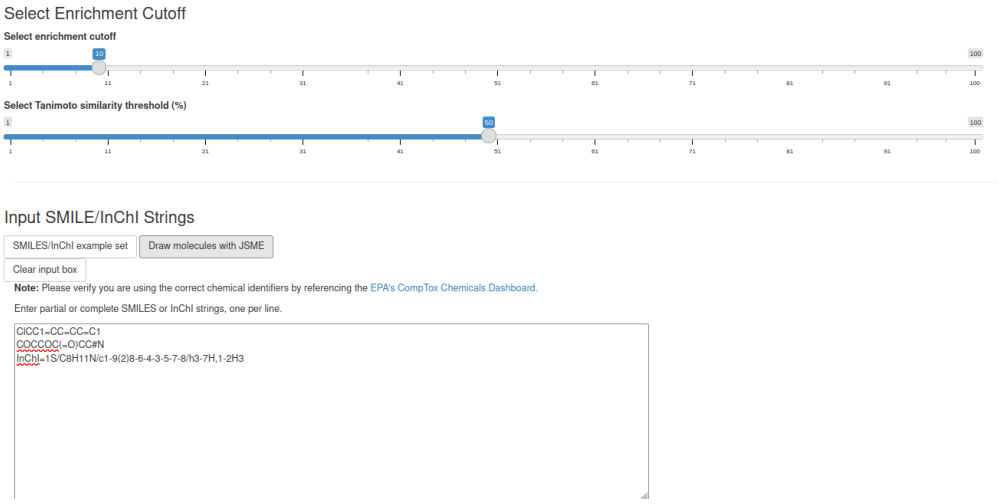


Clicking the **Draw molecules with JSME** button will open the JSME Molecule Editor by Peter Ertl and Bruno Bienfait. Here, you can draw a molecule using the applet's tools. When you are finished drawing, we can right-click in the whitespace of the canvas and select "Copy as SMILES" or "Copy as InChI" and paste the copied text in the input box.

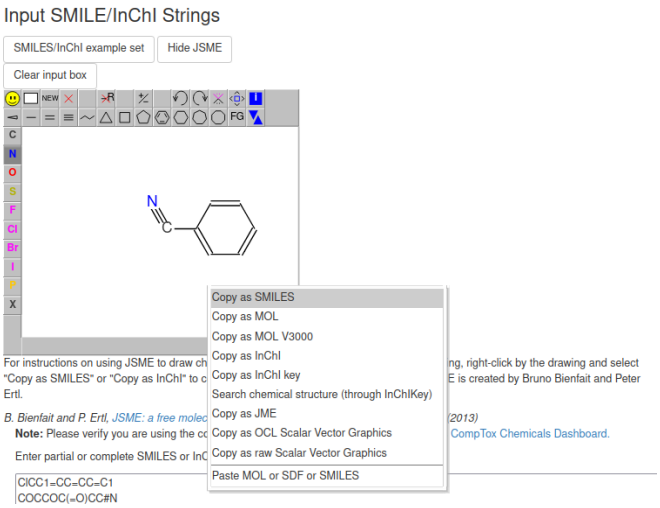


II.2.c. Enrich From Chemicals With Structural Similarity

This enrichment analysis type accepts either SMILES or InChI strings (one per line). Each string is treated as its own data set and will be enriched independently of any other sets provided. SMILES and InChI strings may be mixed: you may perform enrichment with a SMILES string on one line and an InChI string on another. Clicking the **SMILES/InChI example set** button will fill the input box with three chemicals: two SMILES strings and one InChI string. Clicking the **Clear input box** button will reset the input box to a blank state. The **Tanimoto similarity threshold** may be specified using the slider controls above the input box to set the strictness of the search. By default, this is set to 50%.



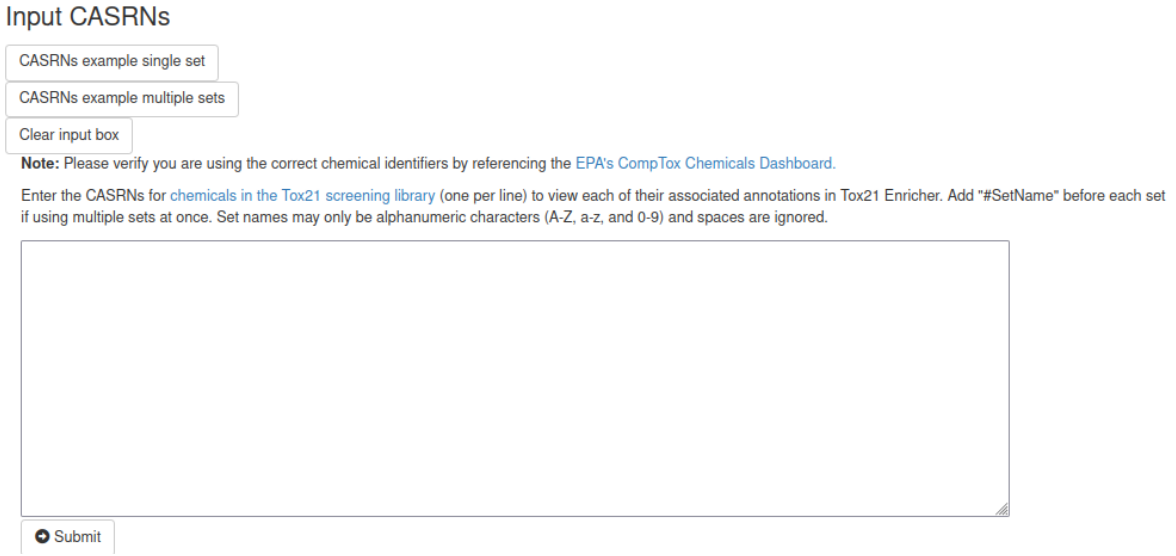
Clicking the **Draw molecules with JSME** button will open the JSME Molecule Editor by Peter Ertl and Bruno Bienfait. Here, you can draw a molecule using the applet's tools. When you are finished drawing, we can right-click in the whitespace of the canvas and select "Copy as SMILES" or "Copy as InChI" and paste the copied text in the input box.



II.2.d. View Annotations for Tox21 Chemicals

This function does not actually perform enrichment analysis; rather, it returns a list of every annotation in the Tox21 database that is associated with each of the supplied chemicals. Like the **User-provided CASRN list** enrichment type, this enrichment analysis type accepts only CASRN strings as input (one CASRN per line). You may find annotations for multiple sets of chemicals at the same time. To use multiple sets, separate lines of CASRN strings with **unique** set names of the form "#SetName" with a pound symbol (#) before the name. Only alphanumeric characters (A-Z, a-z and 0-9) may be used in set names. If you choose to provide names for input sets, **all** sets must be assigned a name. Spaces in set names or CASRN strings are ignored, and extra newline characters between, after, and before lines are also ignored. If no set names are provided, all lines of the input box will be treated as one set and will be assigned the default name of "Set1."

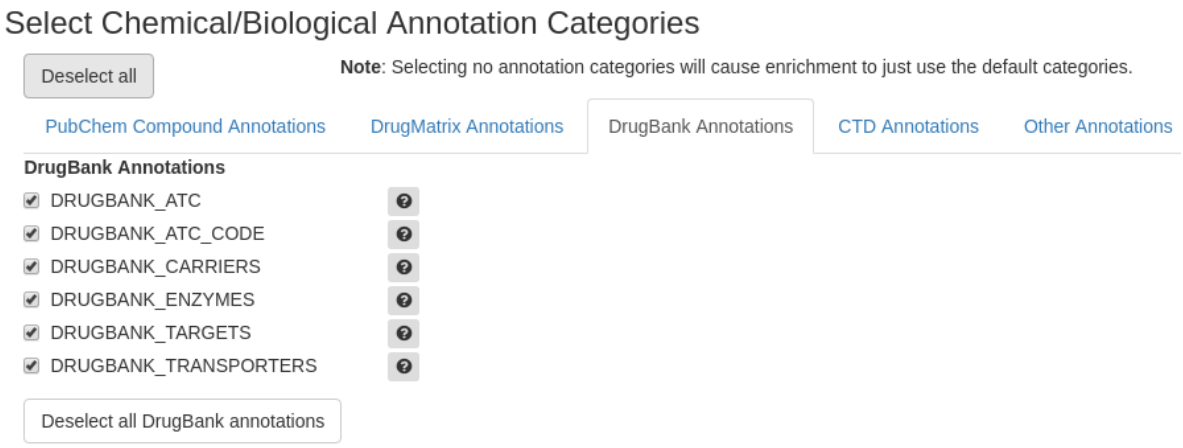
This mode will not provide any annotations for a CASRN if that chemical is not present in the Tox21 screening library. To view all the chemicals in the Tox21 screening library, click the **chemicals in the Tox21 screening library** link which opens the page https://comptox.epa.gov/dashboard/chemical_lists/TOX21SL in a new window.



Clicking the **CASRNs example single set** button will fill the input box with one, unnamed set of CASRNs. Clicking the **CASRNs example multiple sets** button will fill the input box with three sets of CASRNs. Clicking the **Clear input box** button will reset the input box to a blank state.

II.3. Selecting Annotation Categories

The top of the landing page displays lists of annotation categories, separated into five category types**: PubChem Compound Annotations**, **DrugMatrix Annotations**, **DrugBank Annotations**, **CTD Annotations**, and **Other Annotations**. By default, the **PubChem Compound Annotations** tab is selected. You can click on the tabs to view each tab's corresponding annotation categories. Each category name has a checkbox to its left that, when checked, means that the application will attempt to find matching annotations from the given category. The application will ignore any potential results from categories left unchecked. By default, all categories are checked except for the CTD_GOFAT_BIOPROCESS category: using this category can potentially slow down enrichment by a large amount, so it is not recommended to be used in most scenarios. Each category name has a question mark button to its right that, when hovered over, displays additional information about each category. If no categories are selected, the application defaults to just using all the annotation categories (except for CTD_GOFAT_BIOPROCESS).

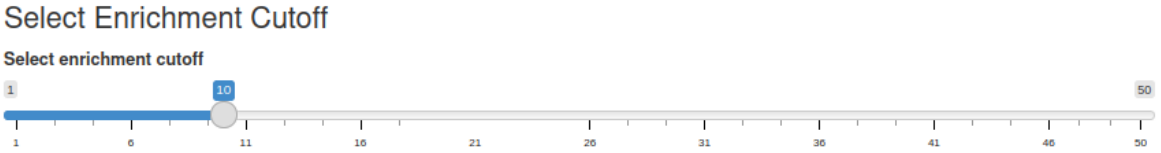


Clicking the **Deselect all/Select all** button will either deselect or select all the annotation categories across all tabs. Note that clicking the **Select all** button will select the CTD_GOFAT_BIOPROCESS category too.

Each tab also has a corresponding button to deselect or select all the annotation categories within the tab. An example can be seen in the image above: clicking the **Deselect all DrugBank annotations** button will deselect only the annotations in the **DrugBank Annotations** tab. Note that clicking the **CTD** tab's corresponding **Select all CTD annotations** button will select the CTD_GOFAT_BIOPROCESS category too.

II.4. Selecting Enrichment Cutoff Value

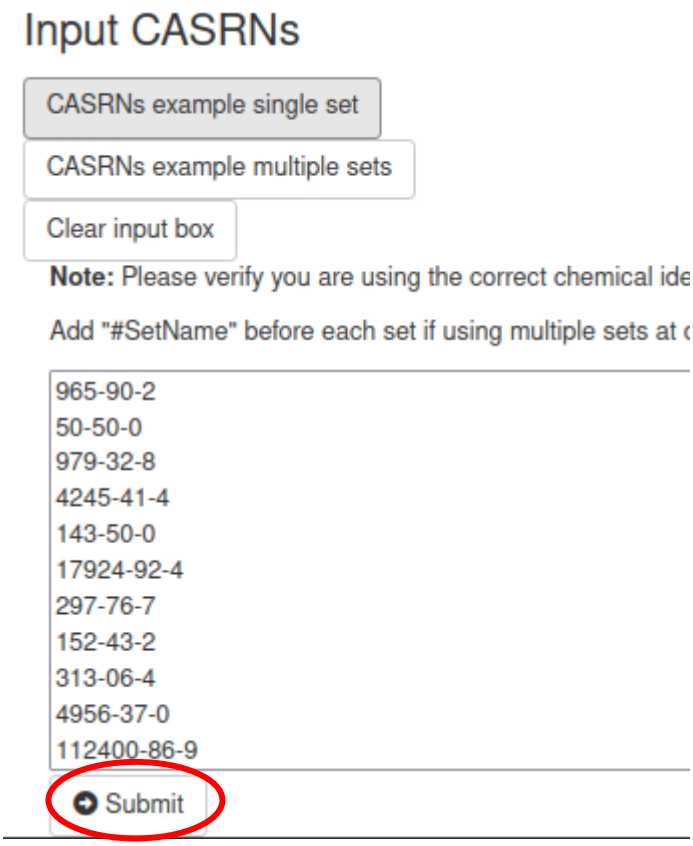
Under the tabs for selecting the appropriate annotation categories, the landing page displays a slider input for specifying the enrichment cutoff value. This value determines the maximum number of enrichment results displayed per data set submitted. By extension, this will also determine the maximum number of nodes displayed during network generation. By default, this is set to 10 and can be increased to a maximum of 50 or decreased to a minimum of 1.



II.5. Performing Enrichment

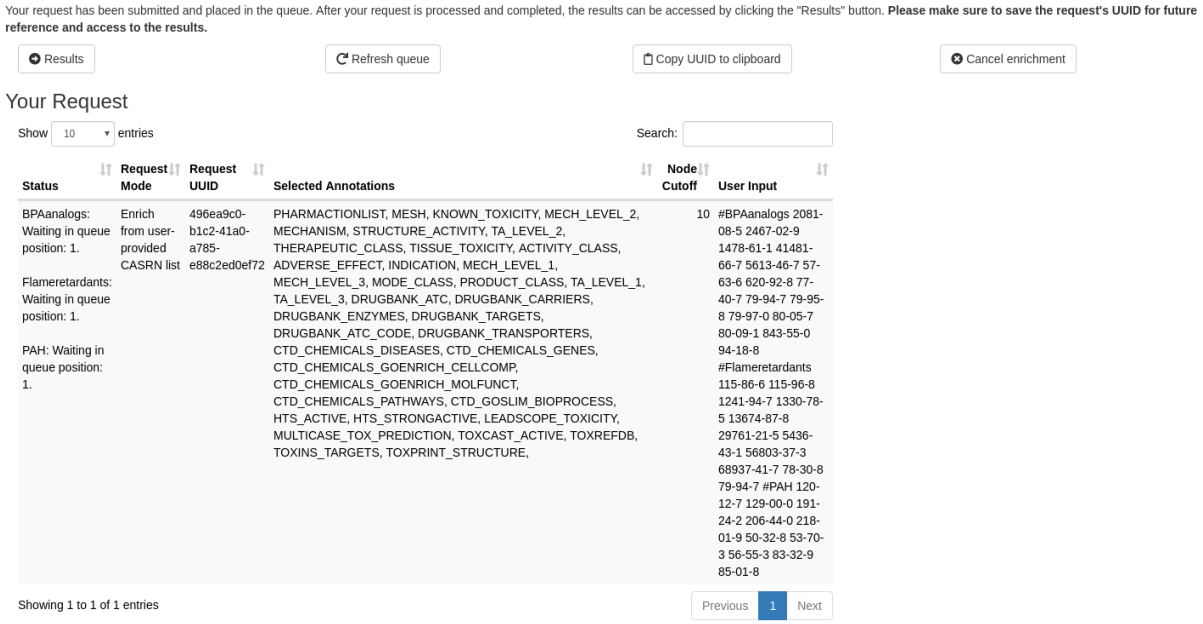
After input has been entered, it is time to begin enrichment. This can be done by clicking on the **Submit** button under the input box. If there are no problems validating your input, you will be sent to the waiting page.

Validation errors may occur if you input a string that is not a properly formatted CASRN, SMILES, or InChI identifier, if you forget to name a set, or if you try to submit a blank input. If a validation error occurs, Tox21 Enricher will display a warning and the request will not proceed.



III. Waiting Page

After submitting your request, you will be taken to the waiting page.

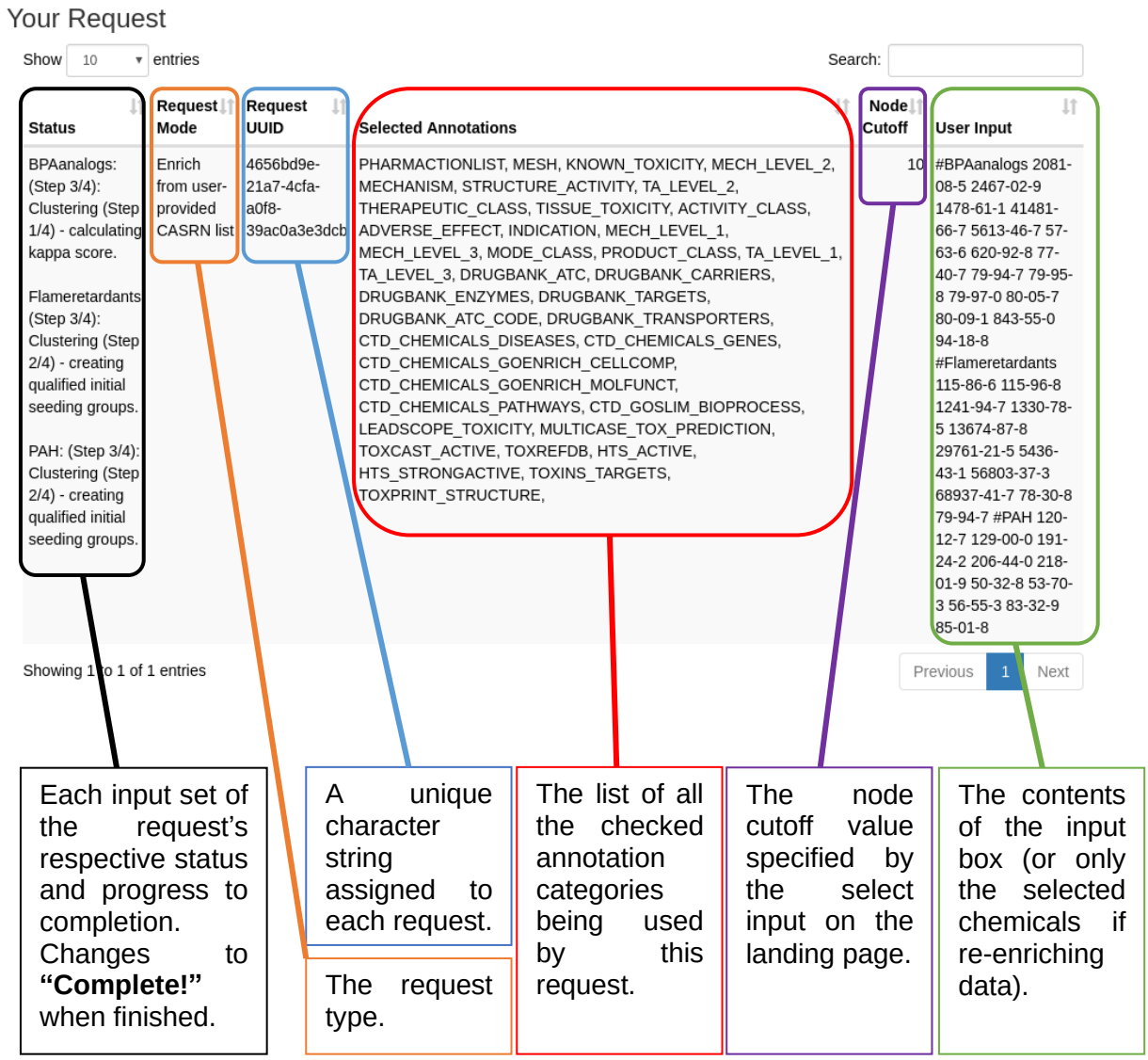


There are four buttons at the top of the waiting page that perform different tasks when clicked:

- **Results** – This will take you to the request's results page if the request has finished. If the request has not yet finished, the waiting page will display a warning.
- **Refresh queue** – This will refresh the **Your Request** table and update the **Status** column.
- **Copy UUID to clipboard** – This will copy your request's UUID to the clipboard so it may be pasted elsewhere.
- **Cancel enrichment** – This will open a prompt to cancel the request. Cancelled requests cannot be recovered. The request's temporary file will be deleted from the client filesystem and records of the request will be deleted from the Tox21 Enricher database.

Please make sure to save your request's UUID somewhere where you may reference it later. Knowing the UUID for a given request is the only way to view the request's results after navigating away from the waiting page.

The **Your Request** table contains some helpful information related to the parameters of your request:



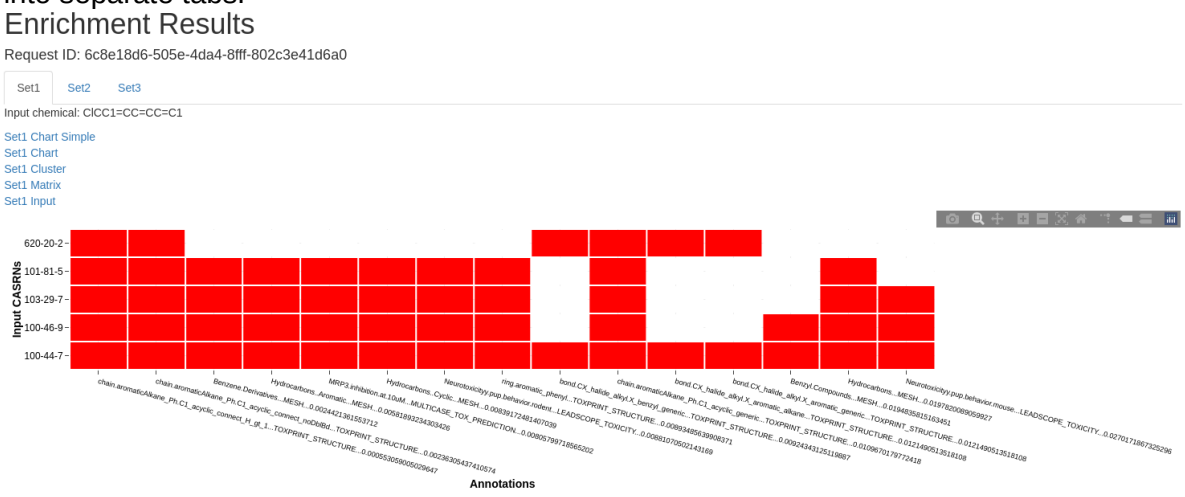
IV. Results Page

IV.1. Enrichment Results

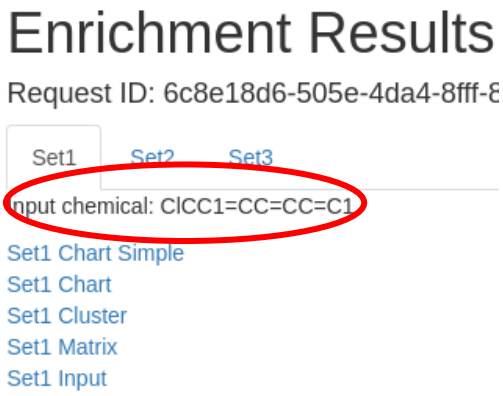
Once your request has completed, you may click the **Results** button to view the request's results.

IV.1.a. Result Files

The top of the results page displays relevant files generated by the enrichment analysis process. If multiple sets were submitted, the files corresponding to each set are organized into separate tabs.



Additionally, if you submitted SMILES or InChI strings for enrichment, the original SMILES/InChI string is displayed with the set's results.

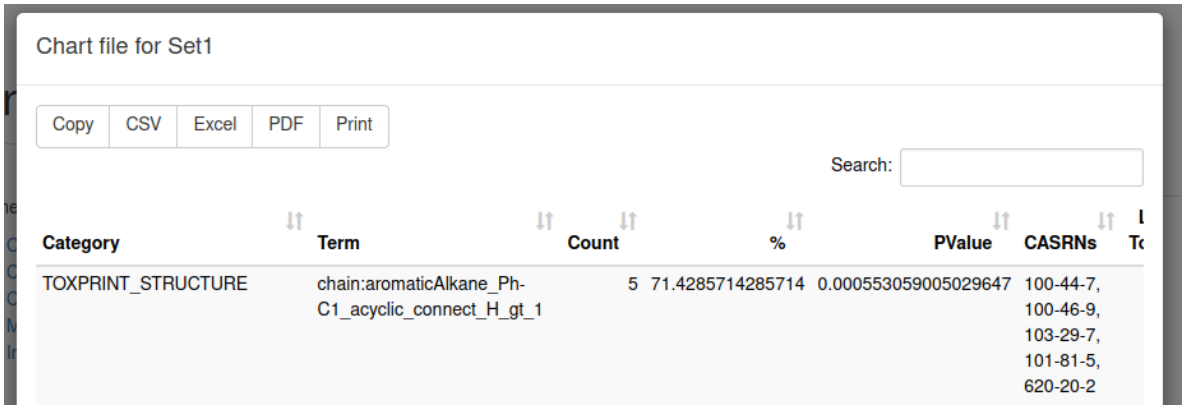


If one could be generated, an interactable heatmap using the Plotly library for R (https://plotly.com/r/) will be displayed under the result file links. A red square signifies that the annotation on the x-axis belongs to the CASRN(s) on the y-axis, while a white square signifies that the annotation is not associated with the CASRN(s) on the y-axis.

Clicking any of the result file links will download a copy of the corresponding file from the Tox21 Enricher server to the client application's temporary cache so that it may be viewed in a table in the client application.

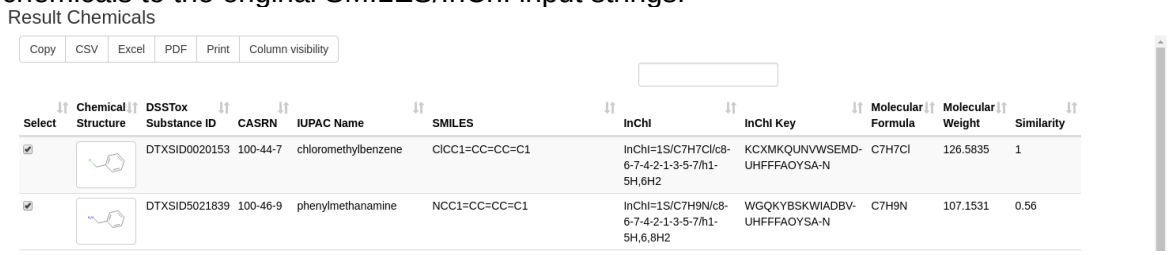
The result files are as follows:

- **<set_name> Chart Simple** – A list of the top 10 most significant annotations for each annotation class (.txt format).
- **<set_name> Chart** – A list of all significant annotations (.txt format).
- **<set_name> Cluster** – A list of significant terms in which functionally similar annotations are grouped together to remove redundancy. This is performed with respect to the whole annotation set rather than to individual annotation classes (.txt format).
- **<set_name> Matrix** – A plaintext representation of the heatmap (.txt format).
- **<set_name> Input** – A plaintext list of the input chemicals for this set (.txt format).
- **<set_name> Error CASRNS** – A list of any submitted or matched CASRNs that were not able to be matched with any annotations.

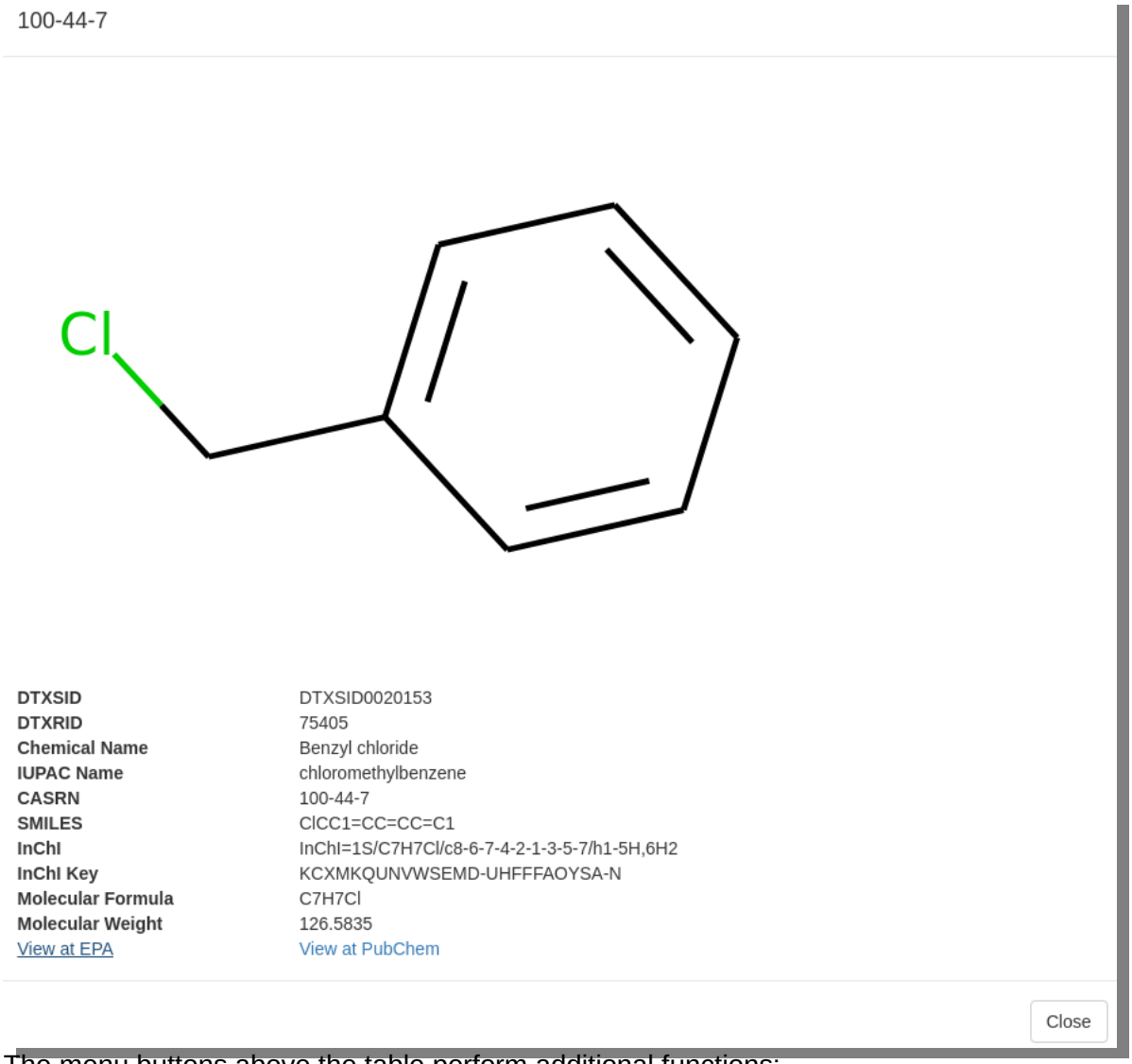


IV.1.b. Result Chemicals

The **Result Chemicals** table is only visible when enriching from chemicals with shared substructures or structural similarity. This table displays information about all of the related chemicals to the original SMILES/InChI input strings.



Additionally, if you performed enrichment from chemicals with structural similarity, an additional column is shown displaying a Tanimoto value describing the similarity of each result chemical to the original input chemical. Clicking the chemical structure image for a given chemical will open a modal that displays a larger image of the chemical structure, additional information about the chemical, and links to view the chemical's entries on the EPA's CompTox Chemicals Dashboard website and the PubChem database.

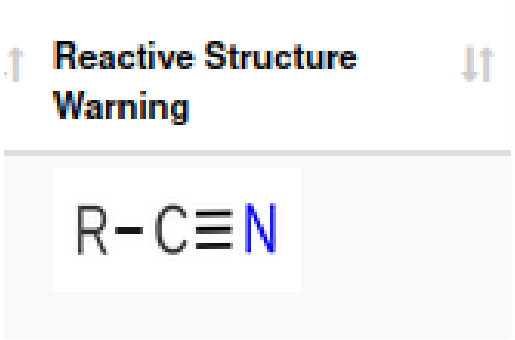


The menu buttons above the table perform additional functions:

- **Copy** – Copies the entire table to the clipboard.
- **CSV** – Allows you to save a copy of the table as a .csv file.
- **Excel** – Allows you to save a copy of the table as an Excel spreadsheet.
- **PDF** – Allows you to save a copy of the table as a .pdf file.
- **Print** – Allows you to print a copy of the table.
- **Column visibility** – Allows you to selectively show or hide certain columns of the table.

Each chemical has an associated checkbox that marks the chemical for re-enrichment. By default, all chemicals' checkboxes are checked.

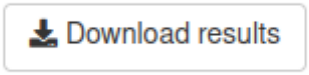
If an originally submitted SMILES/InChI string contains a certain reactive structure, Tox21 Enricher will check to see if each of its related chemicals also contain that structure. If a related chemical does not contain the structure, an additional **Reactive Structure Warning** column is added to the **Result Chemicals** table displaying a picture of the suspect structure. A warning will also be displayed if the original input string does not contain a reactive structure, but one of its related chemicals does. Currently, Tox21 Enricher displays warnings if the following structural groups are detected in either (but not both) the input chemical and one of its related chemicals:



- **Nitrile group (cyanide)**
- **Aldehyde**
- **Epoxide**
- **Isocyanate**

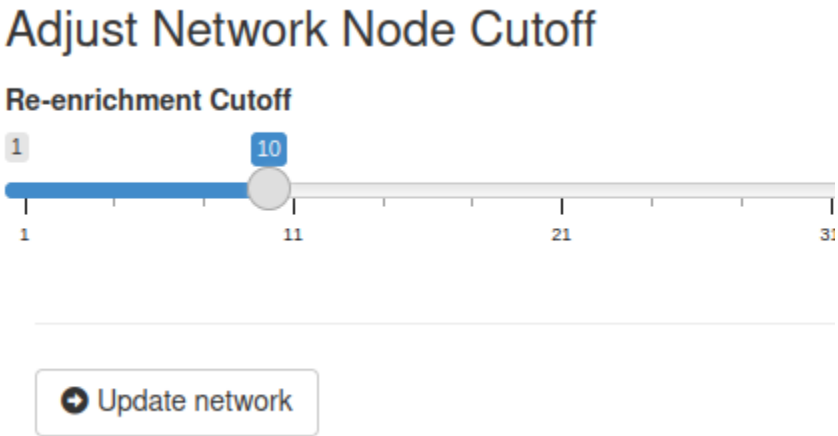
IV.1.c. Download Results Button

Clicking the **Download results** button will prompt you to download a .zip archive of all of the results files for all the sets for a given request.

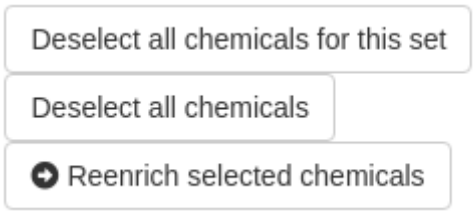


IV.1.d. Adjust Network Node Cutoff & Perform Re-enrichment

Below the result files and chemicals is a series of controls for rerunning enrichment on the result set. First is a slider control for adjusting the node cutoff value so that you may change the number of nodes without having to completely perform enrichment again from scratch.



Under this slider input, there is a button to either update the network (if enriching from a user-provided CASRN list) or perform enrichment again with only the selected result chemicals (if enriching from chemicals with structural similarty or shared substructures). Additionally, if enriching from chemicals with structural similarity or shared substructures, more buttons are present that interact with the **Result Chemicals** table:



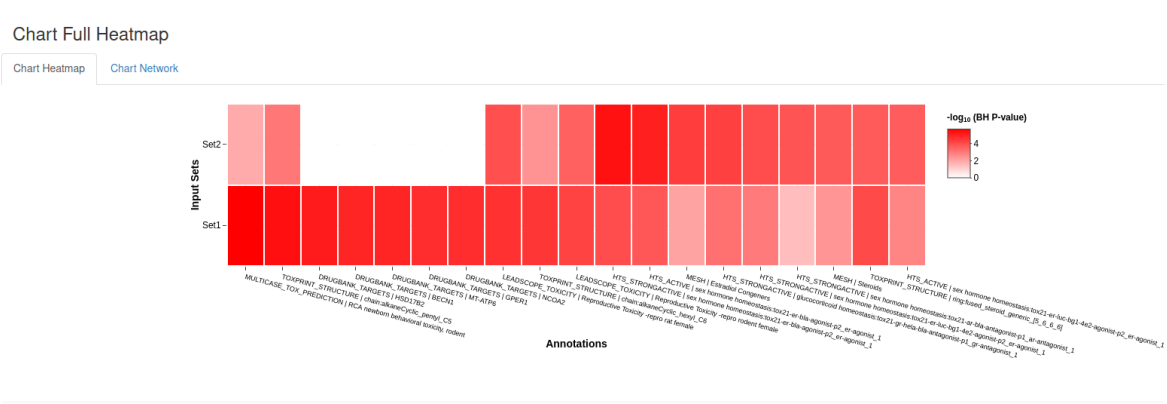
- **Deselect all chemicals for this set** – Deselects all of the result chemicals only for the currently selected tab (result set).
- **Deselect all chemicals** – Deselects all of the result chemicals across all tabs.

Additionally, if any result sets have chemicals with reactive structure warnings, a third 

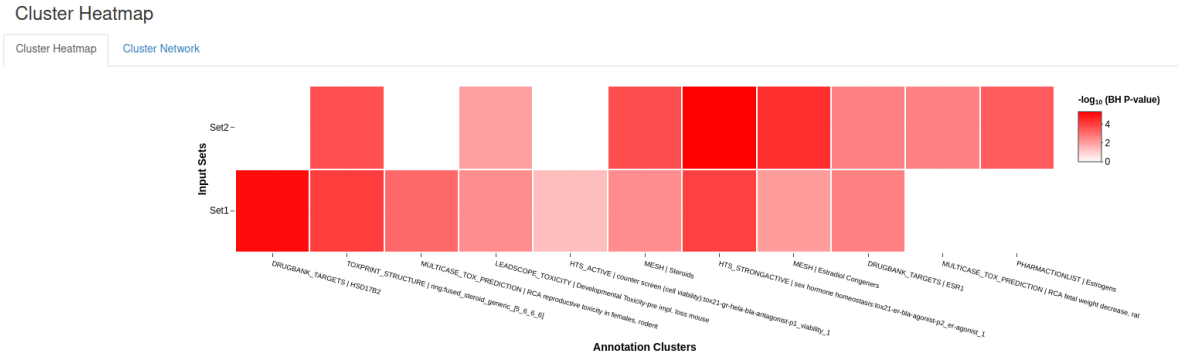
Deselect all chemicals with warnings button will appear. Clicking this button will deselect all chemicals with reactive structure warnings across all tabs.

IV.1.e. Chart and Cluster Heatmaps

Below the re-enrichment and node cutoff controls are interactive heatmaps using the Plotly library for R. The chart heatmap displays the most significant annotations across all the chemicals in each set.



The cluster heatmap displays the most significant annotations across all the chemicals in each set as well, but reduces these annotations down to groups of functionally similar annotations.



IV.1.f. Chart and Cluster Networks

Clicking on the **Chart Network** tab next to the **Chart Heatmap** tab will open the chart network display. Similarly, clicking on the **Cluster Network** tab will open the cluster network display. Both network displays have identical layouts. The nodes correspond to significantly enriched annotations and the edges indicate that there is significant overlap between the two annotations in terms of chemical contents. The edge color gradient indicates the degree of overlap based on a Jaccard index. Note that the network may take some time to load depending on the number of nodes represented.

On the left side, there is a number input for changing the q-value. This is the cutoff value for the statistically significant overlap between pairs of nodes. There are also checkboxes for changing which input sets and/or annotation classes should be represented in the network. Under the **Other Options** section, there is the option to enable network physics, which will make the nodes physically react with each other. There is also the option to toggle curve smoothing for the network edges. This is enabled by default, but disabling it may improve performance. Clicking the **Update network** button will regenerate the network, reflecting any changes made to selected input sets, physics, or the q-value.

In the middle of the network display, there are two drop-down menus. The top menu allows you to select certain annotations in the network without having to click on the nodes in the network. The bottom menu allows you to hide all annotations not of the selected category, making the network easier to navigate and read. Below these menus is a legend that shows each category's unique color.

You may interact with the network by clicking and dragging nodes around the canvas. The mouse wheel can be used to zoom in and out of the network view as well. Additionally, the green buttons overlaid on the network may also be clicked to manipulate the network view. Under the network, there is the **Export as png** button which allows you to save an image of the network as a .png file.

Under the **More Information for Selected Annotation** section, you will see a prompt to select any node in the network. Doing this will display a link to an external website or database with more details about the annotation in the selected node.

Under the **Overlapping Chemicals** section, you will see a prompt to select any edge in the network. Doing this will generate a Venn diagram under the network detailing the number of chemicals shared and unique to the annotations displayed in the connecting nodes of the selected edge. Clicking an edge will also generate buttons that will allow you to view a list of all the chemicals (as CASRNs) associated with either of the two given annotations. A third button will also be generated that will allow you to view a list of all the chemicals (as CASRNs) that are associated with both given annotations. Underneath these buttons are links that allow you to save the Venn diagram as a .png image or .pdf document when clicked.

Chart Full Heatmap

Chart Heatmap | Chart Network

Edge Selection Criteria

Q-value

0.05

Selected Input Sets

- [x] BPAanalogs
- [x] Flameretardants
- [x] PAH

Selected Annotation Classes

- [x] TOXPRINT_STRUCTURE
- [x] HTS_ACTIVE
- [x] TOXCAST_ACTIVE
- [x] HTS_STRONGACTIVE
- [x] MESH
- [x] LEADSCOPE_TOXICITY
- [x] MULTICASE_TOX_PREDICTION
- [x] TOXINS_TARGETS
- [x] CTD_CHEMICALS_GENES

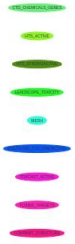
Other Options

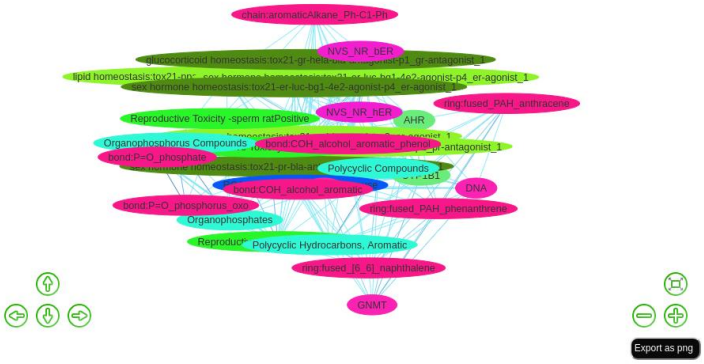
- [ ] Enable physics?
- [x] Smooth curve for edges?

Update network

Select by id

Select by group





More Information for Selected Annotation

Click on any **node** to view additional information for the annotation in the selected node.

Overlapping Chemicals

Click on any **edge** to view a Venn diagram of the chemicals associated with the annotations in its two nodes.

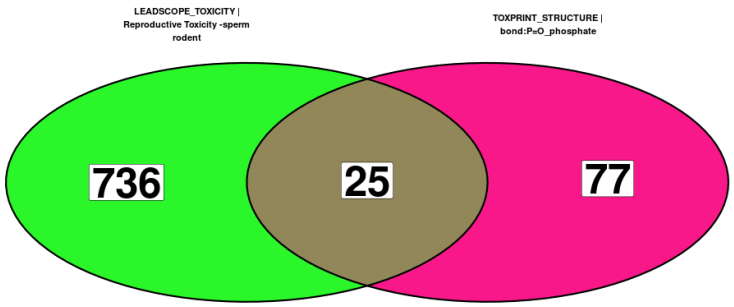
View chemicals for LEADSCOPE_TOXICITY | Reproductive Toxicity -sperm rodent

View chemicals for TOXPRINT_STRUCTURE | bond:P=O_phosphate

View shared chemicals

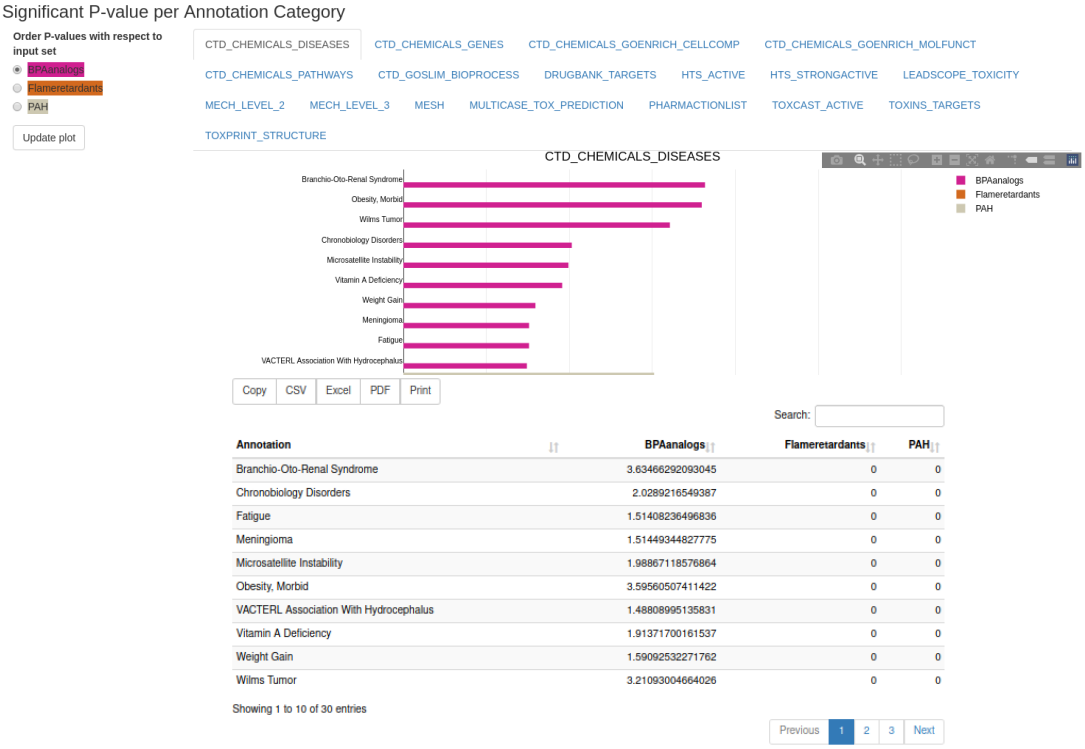
Download plot as .png

Download plot as .pdf



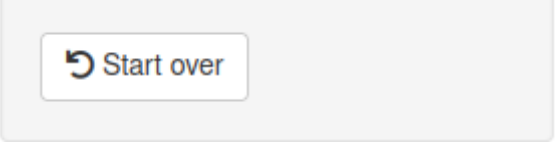
IV.1.g. Significant P-value per Annotation Category Bar Graphs

At the bottom of the results page, you can find a series of bar graphs that display all the significant annotations across all result sets and each set's inverse p-value for each annotation, if applicable. Separate bar graphs are created for each annotation category and are put into each category's respective tab. A color legend appears on the righthand side of each bar graph if multiple sets are represented. Clicking on a set name in this legend will hide its trace from the graph, while double-clicking a set name will hide all other sets' traces. To the left of the bar graphs is a menu that allows you to select one set to order values by. Clicking the **Update plot** button will update all the bar graphs to be ordered with respect to the selected set. Trace colors are unique for each set and are randomly selected from a predefined list each time enrichment is performed. Bar graphs are always ordered with the most significant value for the selected set at the top and the least significant value for the selected set at the bottom. The data in each bar graph are also represented in a table below each bar graph. Each table may be saved in different formats by using the buttons above each table.



IV.1.h. Start Over Button

After enrichment is successfully performed, the **Start over** button is added to the bottom of the sidebar. Clicking this button will take you back to the landing page. This button is functionally identical to refreshing the application from within an internet browser.

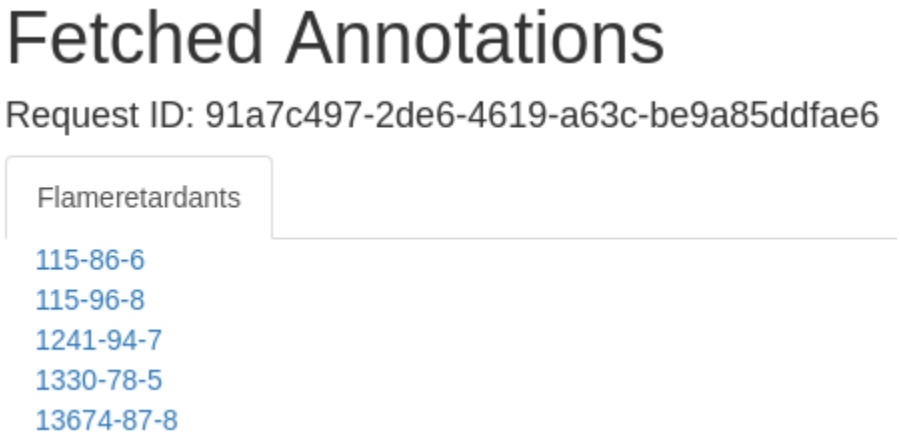


IV.2. Annotation Results

IV.2.a. Result Files

The top of the results page displays relevant files generated when fetching annotations. If multiple sets were submitted, the files corresponding to each set are organized into separate tabs.

Each submitted CASRN will have its own text file with a name of the form **<casrn>**. This file will contain all of the annotations in the Tox21 Enricher database that are associated with the submitted chemical.



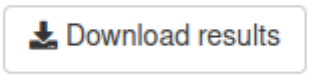
The annotations in this file are organized so that each line contains one complete annotation: the category the annotation belongs to is on the left and the annotation's name is on the right, and they are separated by a tab. If Tox21 Enricher could not find any associated annotations for a submitted CASRN, the CASRN will be ignored and a corresponding result file will not be generated. The annotation-fetching process will only search through the annotation categories that were checked on the landing page.

An additional text file of the **name <set_name> Full Matrix** will be generated for each submitted set of CASRNs. This file contains a plaintext representation of a matrix of all the fetched annotations in the set and if they are associated with each of the submitted CASRNs.

Much like when performing enrichment, The input file will be displayed here with the name **<set_name> Input**. If any CASRNs produced errors or did not match any annotations in the database, a file will be produced called **<set_name> Error CASRNs** listing the problem chemicals.

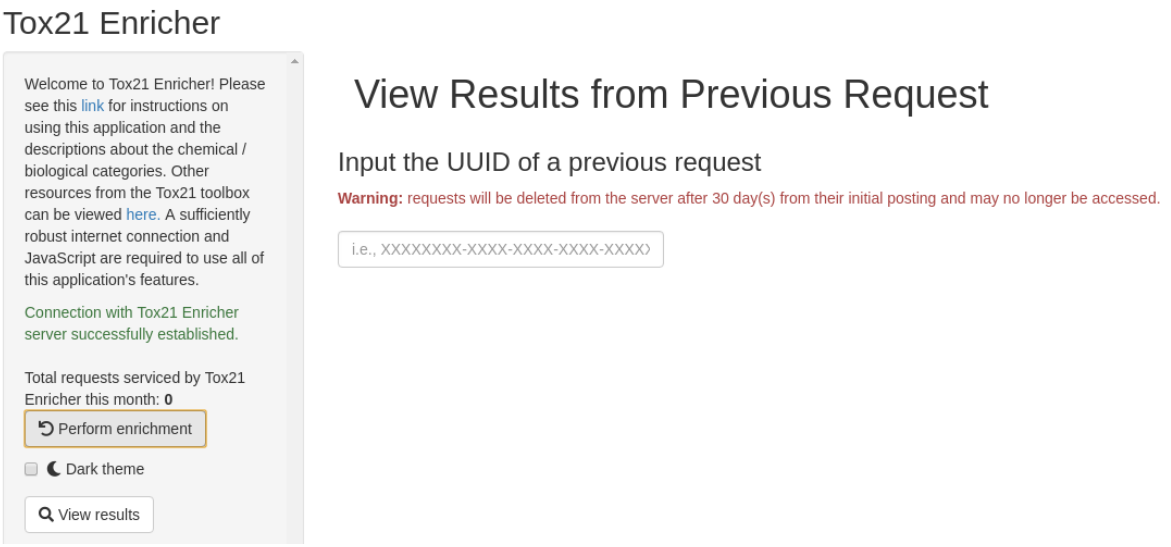
IV.2.b. Download Results Button

Clicking the **Download results** button will prompt you to download a .zip archive of all of the results files for all the sets for a given request.



V. View Results From Previous Request Page

Clicking the **View previous results** button on the sidebar will take you to the **View Results from Previous Request** page.



You may input the UUID of a previous request in the text input box, labeled **Input the UUID of a previous request**. You can then select the **View results** button in the sidebar. If the request exists and has completed, you will be redirected to the results page of the request. Please note that records for all submitted requests will be deleted after a certain number of days have passed since the request was posted. The exact number of days may be configured by the host of the Tox21 Enricher API. After a request's records are deleted, you may no longer use this page to view its result files.

VI. Headless Mode

A user may make direct calls to the Tox21 Enricher API to perform enrichment, fetch annotations, and download results without using the client application's graphical user interface (GUI). The recommended tool for accessing the API from the command line is **cURL**. To make a request, use the cURL command:

```
curl --header "Content-Type: application/json" --request POST -data
'{"mode":"<mode>", "input":"<input_string>",
"annotations":"<annotation_class_list>", "cutoff":<cutoff>,
"tanimoto":<tanimoto>}' http://<server_address>:<port_api_is_running_on>/submit
```

Where:

- **<mode>** is the type of request (casrn, substructure, similarity, or annotation)
- **<input_string>** is a newline (\n)-separated string of input chemical identifiers. If inputting multiple sets of CASRNs, also include set names with a pound symbol (#) in front of each name.
    - Make sure you are submitting the correct identifier for the type of request you are making (i.e., CASRNs for "casrn" and "annotation" and SMILES or InChI strings for "substructure" and "similarity"). Also, if submitting CASRNs, make sure you are using the correct chemical identifiers as included in the EPA's CompTox Chemicals Dashboard: https://comptox.epa.gov/dashboard.
    - For example, for the mode "casrn," you could input something like: `#Set1\n965-90-2\n50-50-0\n#Set2\n4245-41-4\n143-50-0\n17924-92-4`
    - For example, for the mode "similarity," you could input something like: `ClCC1=CC=CC=C1\nN#CSCC1=CC=CC=C1`
- **<annotation_class_list>** is a comma-separated string of annotation class names. This denotes which annotation classes should be included when matching annotations to the input.
    - For example, you could input something like: `MESH,PHARMACTIONLIST,ACTIVITY_CLASS,ADVERSE_EFFECT,INDICATION`
    - You may run the command `curl http://<server_address>:<port>/annotationList` to view a list of all available annotation classes.
    - If not supplied, this value will default to all available annotation classes except for **CTD_GOFAT_BIOPROCESS**.
- **<cutoff>** is the integer value that determines the maximum number of annotations per annotation class to include in things like the network and ChartSimple files.
    - This must be an integer between 1 and 50 inclusive.
    - If not supplied, this will default to 10.
- **<tanimoto>** is the float value that determines the Tanimoto threshold. If a chemical's similarity score is greater than this value, it will be excluded from enrichment analysis.
    - This is only used with the "similarity" mode and will be ignored if supplied with another mode.
    - If not supplied, this will default to 0.5.

Once a request is made, it will be placed in the queue like any other request made from the client application. If the request was successfully made, cURL will return the newly assigned UUID of the request in the terminal.

To check the status of the request, you may run the cURL command:
`curl http://<server>:<port>/completed?<uuid>`. This function will either return a 0 if the request has not completed or a 1 if the request has completed.

To download the results once the request is completed, you may run the cURL command:
`curl http://<server>:<port>/download?<uuid> > <name_of_downloaded_file>.zip`.
This will download a zipped folder containing all the request's results to the file <name_of_downloaded_file>.zip in the current working directory. This request will fail if the request has not yet completed. You may also use this command to download the results of any request, even those that were initially submitted using the client application's GUI.

Examples for using Tox21 Enricher's headless mode can be found in the project's GitHub repository (https://github.com/hurlab/tox21enricher) at <project_root>/demos/. You may need to run the command `sed -i -e 's/\r$//'` on the bash scripts in this folder if you have first cloned the repository to a Windows machine, as Windows will insert different newline characters into the scripts.

VII. Common Issues

Both the client and server code for Tox21 Enricher are still in continued development, so there are likely issues that may arise when trying to either perform certain tasks or set up the application. Known bugs in the code and planned features are documented on the project's GitHub repository at: https://github.com/hurlab/tox21enricher/issues. Other known issues not necessarily related to the code itself are documented in this section of the manual.

VII.1. Runtime Issues

This section intentionally left blank and will be updated in the future.

VIII. Resources

Below are a few resources that users may find helpful:

Name	Link	Description
CompTox Chemicals Dashboard	https://comptox.epa.gov/dashboard	Reference for chemical identifiers to be used in Tox21 Enricher.
Hurlab Server	http://hurlab.med.und.edu/tox21enricher/	Location of Tox21 Enricher on the Hurlab web server.
RDKit	https://www.rdkit.org/docs/index.html	Documentation for the RDKit cheminformatics tool.
Tox21 Enricher GitHub Repository	https://github.com/hurlab/tox21enricher	Tox21 Enricher public GitHub repository.
Toxicology in the 21st Century	https://tox21.gov/	Information regarding the Tox21 data set.

IX. References

B. Bienfait and P. Ertl, JSME: a free molecule editor in JavaScript, J. Cheminformatics 5:24 (2013)

END OF THE USER'S MANUAL