Toxicity Predictor

(LIVER/MIE-QSAR & LUNG/MIE-QSAR)

User Guide

July 2021 Ver.1.5

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1. System overview

Toxicity Predictor is a QSAR system that predicts 59 types of molecular initiating events (MIE) in adverse outcome pathway (AOP), drug induced liver injuries (DILI) and drug induced pulmonary toxicities (DIPT) against input compounds. The prediction models are constructed by machine learning using activity data from PubChem and reported side effects data from JAPIC AERS. It also provides reported side effects data of similar medicines. Users can input compounds through a molecular editor on their web browsers, or by uploading SDF files or list of SMILES.

2. Recommended system requirements

The recommended web browsers and versions are as follows.

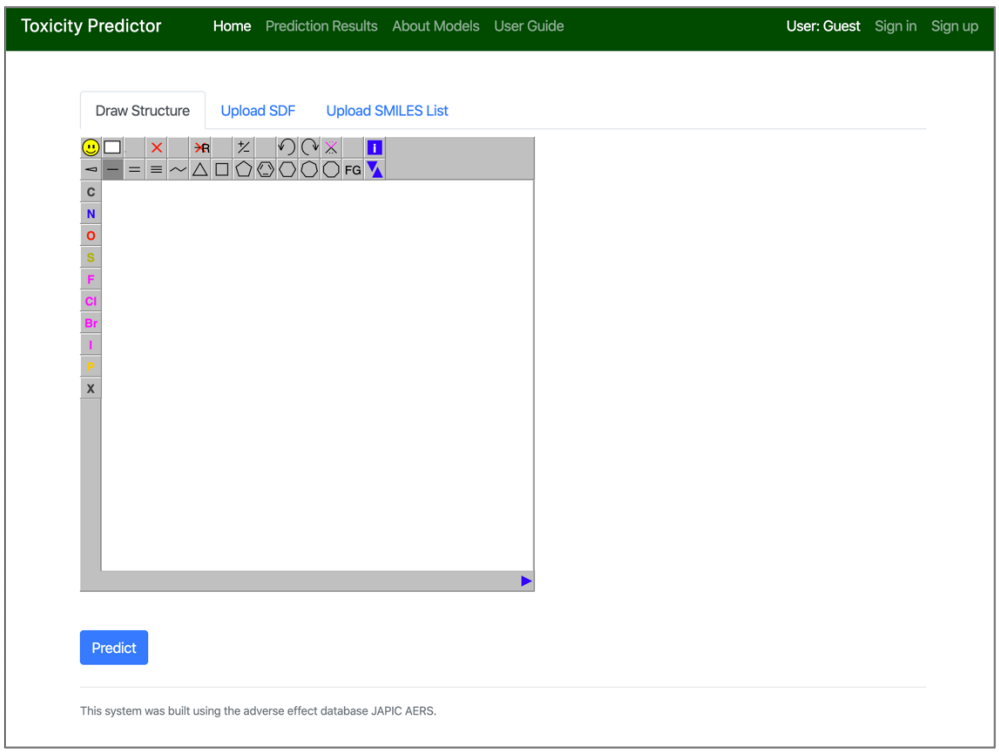
Web browser	**Version**
Google Chrome	78.0 and up
Firefox	70.0 and up
Safari	12.0.3 and up
Microsoft Edge	44 and up
Internet Explorer	11 and up

3. Usage

In this chapter, we explain usage of Toxicity Predictor.

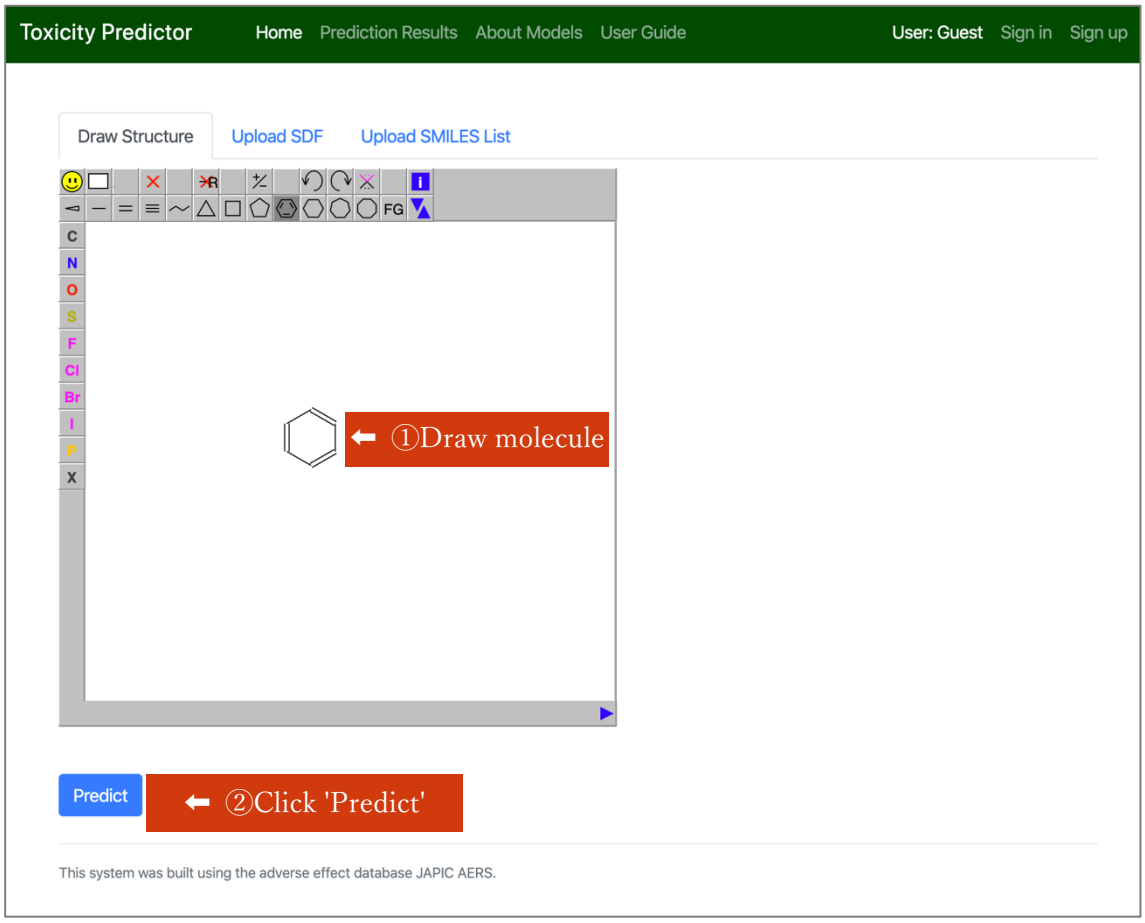
3.1. Home page

When you access to the URL of Toxicity Predictor (http://mmi-03.my-pharm.ac.jp/tox1/), you can see the following home page。In this page, you can input compounds to predict. Compounds can be input by drawing structures on the molecular editor, paste single SMILES, uploading an SDF file or uploading a list of SMILES.



3.1.1. Drawing structures

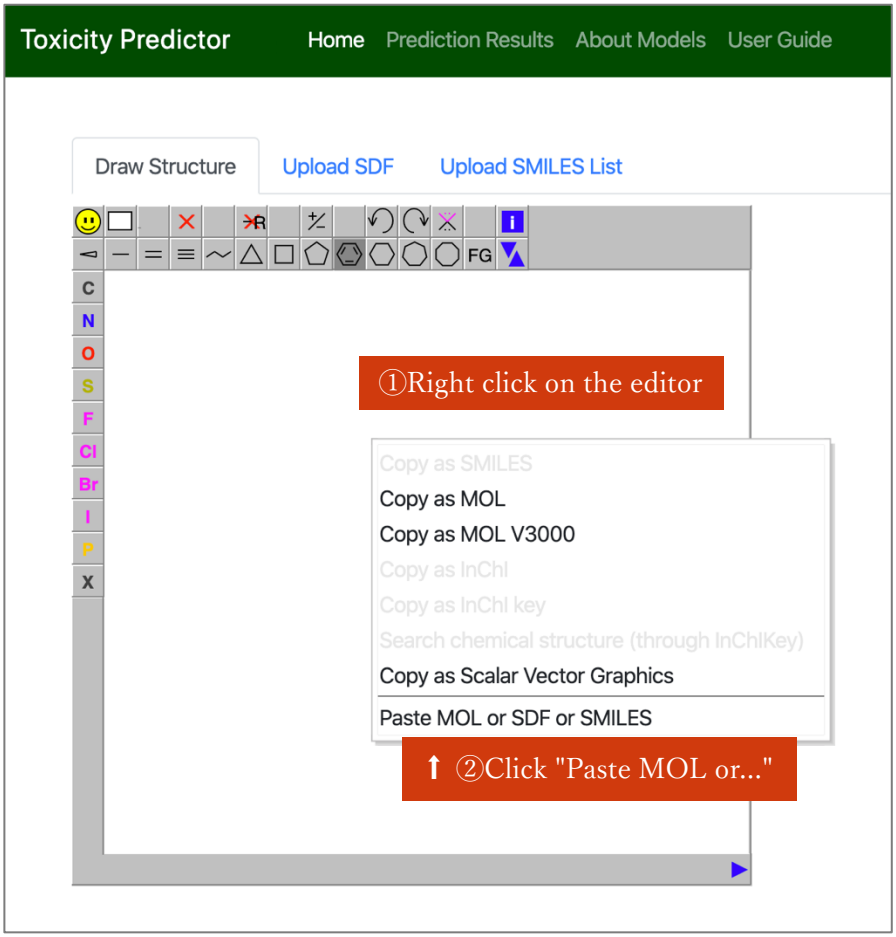
On the molecular editor, you can draw a two-dimensional structure of a compound to predict. After drawing, click 'Predict' button as the following screen shot. After clicking, the web browser will navigate to the Prediction Result page (see section 3.2).

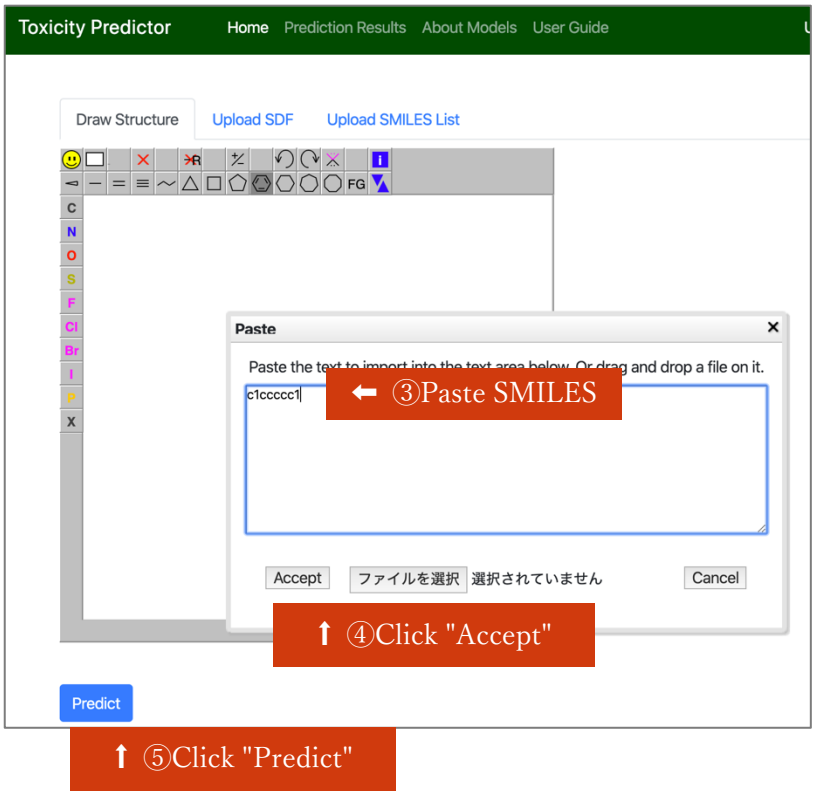


3.1.2. Input single SMILES

If you have a SMILES you want to predict, please ①right click on the molecular editor to show the menu, ②click "Paste MOL or SDF or SMILES", ③paste SMILES on the window shown and ④click "Accept" button. Please check that the pasted SMILES is shown on the molecular editor as a two-dimensional structure, then ⑤click "Predict" button. After clicking, the web browser will navigate to the Prediction Result page (see section 3.2) .

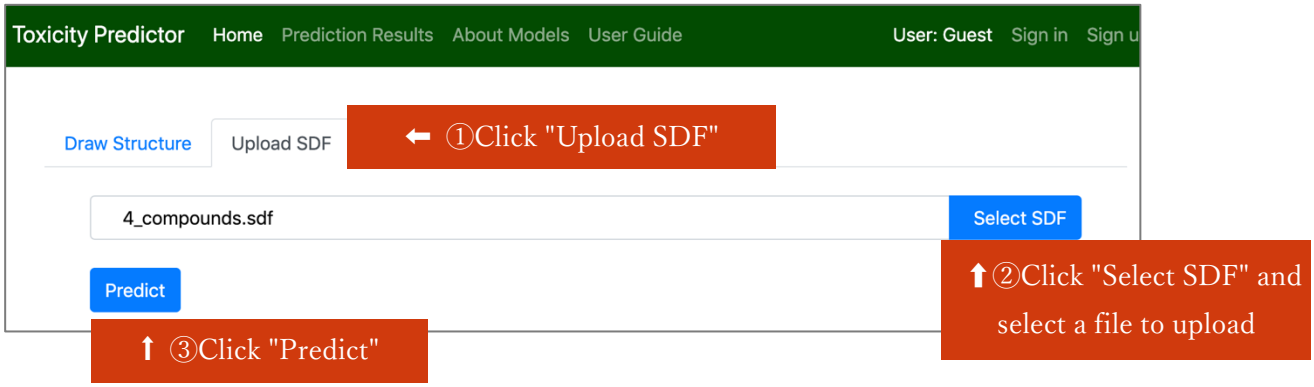
You can paste a MOL format and an SDF format as wells as SMILES in this way, however, if you paste a SDF format, only the first compound in SDF are input. If you want to upload multiple compounds at the same time, please upload your SDF as a file (see item 3.2) or upload smiles list as a file (see item 3.1.4) .


Toxicity Predictor
Home
Prediction Results
About Models
User Guide
Draw Structure
Upload SDF
Upload SMILES List
①Right click on the editor
Copy as SMILES
Copy as MOL
Copy as MOL V3000
Copy as InChI
Copy as InChI key
Search chemical structure (through InChIKey)
Copy as Scalar Vector Graphics
Paste MOL or SDF or SMILES
② Click "Paste MOL or..."


Toxicity Predictor
Home
Prediction Results
About Models
User Guide
Draw Structure
Upload SDF
Upload SMILES List
Paste
Paste the text to import into the text area below. Or drag and drop a file on it.
c1ccccc1
③Paste SMILES
Accept
ファイルを選択
選択されていません
Cancel
④Click "Accept"
Predict
⑤Click "Predict"

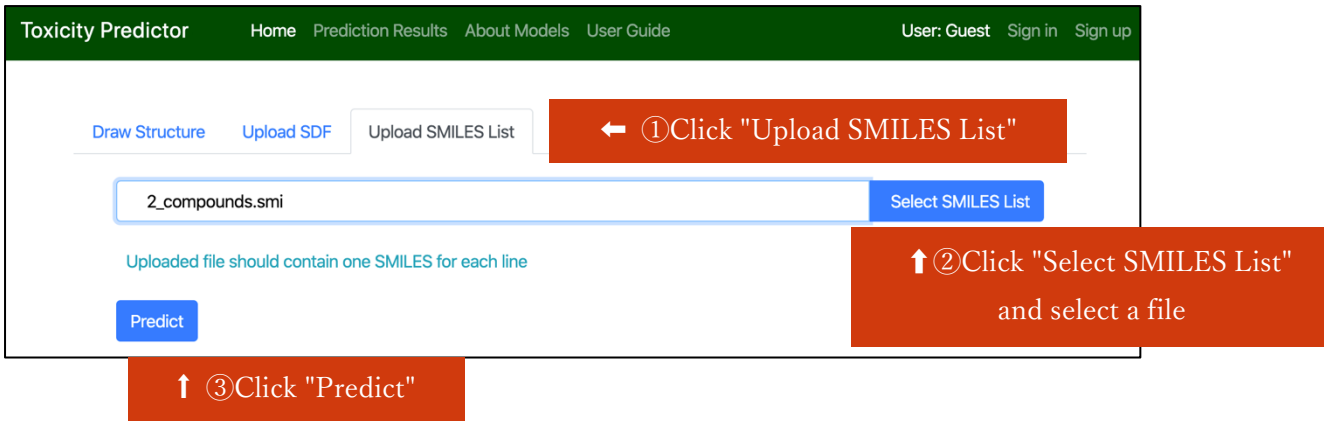
3.1.3. Upload SDF file

By uploading an SDF file, you can start prediction of toxicity against multiple compounds at the same time. Note that the maximum number of predictions allowed for one user is limited up to 100. To upload SDF, please ①click "Upload SDF" to switch the tab, ②click "Select SDF" button to select a SDF file to upload and ③click "Predict". After clicking, the web browser will navigate to the Prediction Result page (see section 3.2).



3.1.4. Upload SMILES list

Instead of uploading an SDF file, you can also upload SMILES list to start multiple predictions. A file to be uploaded a SMILES list should exact one SMILES on each line. Note that the maximum number of predictions allowed for one user is limited up to 100. To upload a SMILES list, please ①click "Upload SMILES List" to switch the tab, ②click "Select SMILES List" to select a file to upload, then ③click "Predict" button. After clicking, the web browser will navigate to the Prediction Result page (see section 3.2).

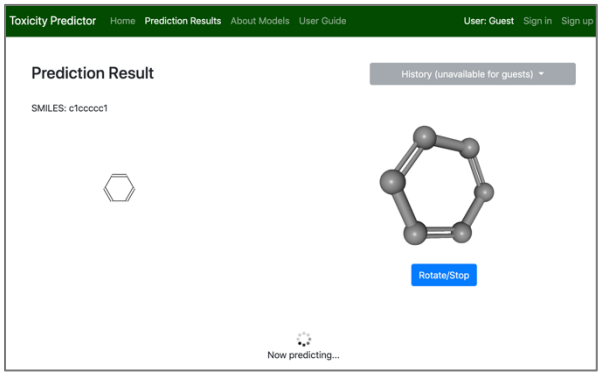


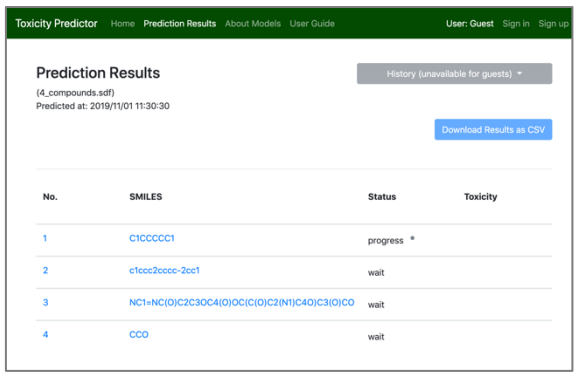
3.2. Prediction Results

On the "Prediction Results" page, you can see the results of toxicity prediction you performed. The web browser automatically navigates to this page after you start prediction. In addition, you can manually move to this page by clicking "Prediction Results" on the header menu on the top of each page.

3.2.1. Wait completion of prediction

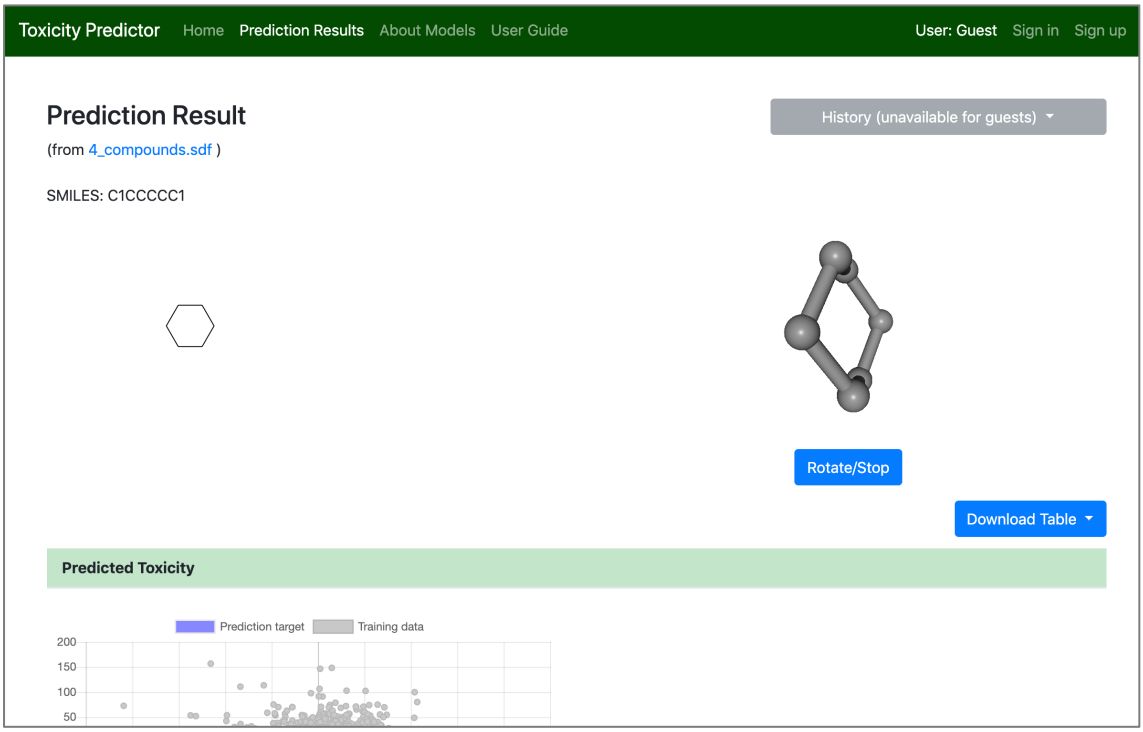
After you started prediction, first you will see a waiting page as the following screen shots. If you input single compound, you will see the page like the left screen shot, otherwise you will see the right one. It takes about 1 minute to predict toxicity of one compound. Note that total time depends on the traffic condition of the server and the size of input compounds.



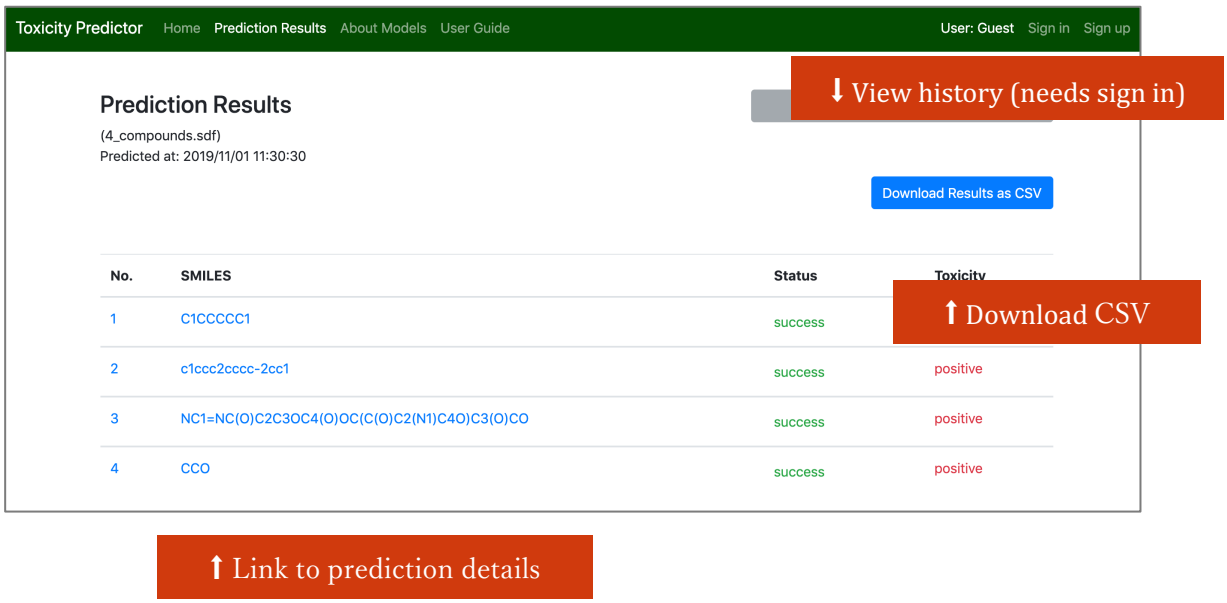


3.2.2. Check prediction results

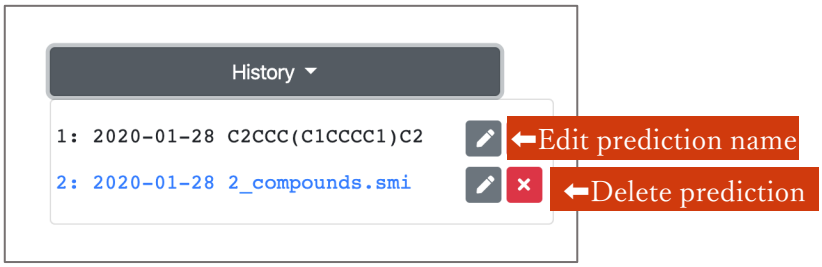
After a prediction completed, the result of the prediction will be shown. If you input single compound, the detail of the prediction result will be shown right away as the following screen shot. Please see item 3.2.3 and up for the explanation of this view.



On the other hand, if you upload multiple compounds, the status of prediction for each compound will be shown as the following screenshot. After a prediction completed, the "Status" column will change to "success". After it changes to "success", you can click the "No." column or the "SMILES" column to move to the detail page of the prediction. After all prediction are completed, you can download a list of prediction result in a CSV file （see section 3.2.6 for the contents of CSVs）. If you signed in this system (see section 3.4), you can also view your history of predictions by clicking the upper right "History" button.

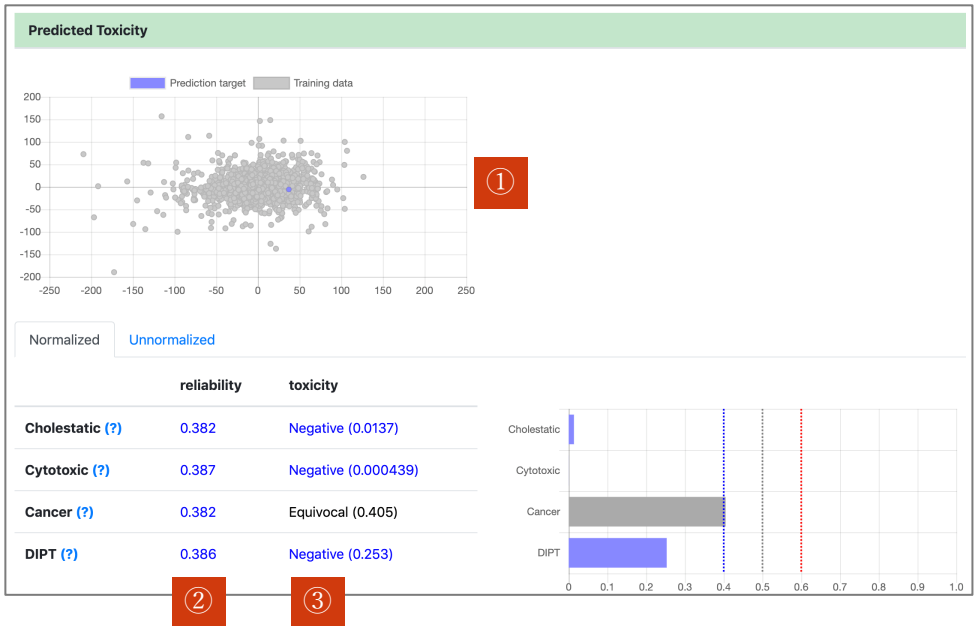


If you click the "History" button, you can see list of file names and SMILES you input so far. If you click a name of a history, you can move to the prediction result page of the past prediction. In this window, you can also edit a name of a prediction by clicking the  button. You can also delete your prediction by clicking the  button.



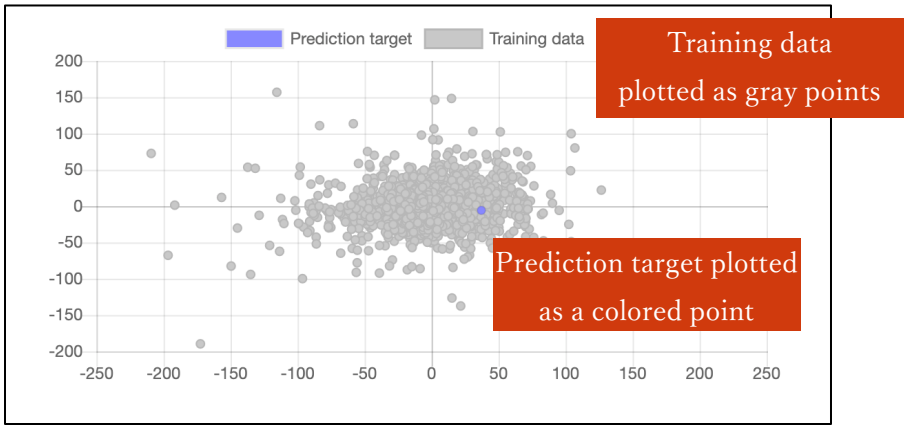
3.2.3. Prediction results of DILI and DIPT

On the top of the prediction detail page, you can see the prediction results of liver injuries and pulmonary toxicities. The contents of this part are a ①scatter plot of trained datasets and prediction target, ②reliability of prediction and ③predicted toxicity.



①The scatter plot of trained datasets and prediction target shows the overview of position of the prediction target among the trained dataset. In this scatter plot, the trained data are plotted as gray points and the prediction target is plotted as a colored point. The coordinate of each point is computed by dimensional reduction of the high-dimensional

Euclidean space that includes corresponding molecular descriptors as data points. The point of prediction target is colored Green (for known compounds), blue (reliability: high), red (reliability: low) depending on the value of ②reliability. The reliability is computed based on the geometric mean of Euclidean distance between the prediction target and the k-nearest training data points.



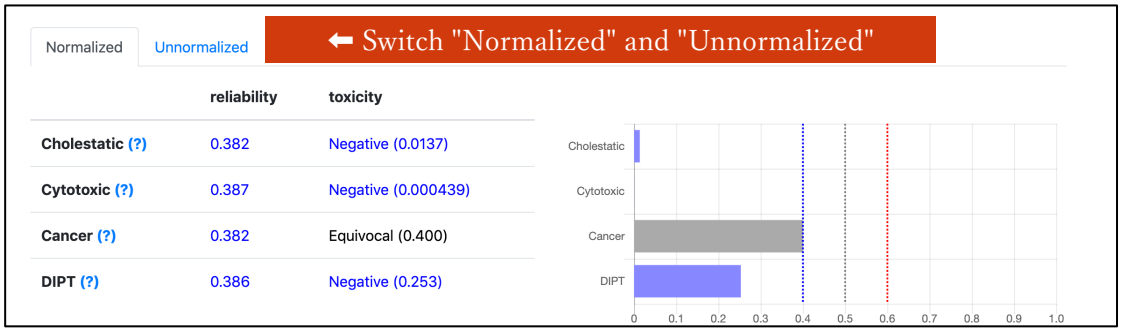
③The predicted toxicity is shown in a numeric value and a bar chart. The types of predicted toxicities are as the following table. You can check the performance of prediction models (see section 3.3) by clicking "(?)" links on the right of the name of the toxicities.

Short name	Description
Cholestatic	Cholestatic Liver Injury
Cytotoxic	Cytotoxic Liver Injury
Cancer	Liver Cancer
DIPT	Drug-Induced Pulmonary Toxicity

This system provides two tabs of prediction results, the "Normalized" tab and the "Unnormalized" tab. By default, the "Normalized" tab is selected. In the "Normalized" tab, the values x_n are shown which is obtained by normalizing the direct predicted value x_u using the following equation. Here, c is the cutoff value of each prediction model based on Youden Index of ROC curve).

$$x_n := x_u^{-\log_c 2}$$

By clicking the "Unnormalized" tab, you can see the predicted value x_u without normalization.



In this table, the predicted value is colored depending on the value of x_n. If $x_n < 0.4$, the value is shown as Negative (blue), Equivocal（black）if $0.4 \leqq x_n \leqq 0.6$, Positive（赤） if $0.6 \leqq x_n$. If the input compound is included by training data, the experimented value is shown instead of the predicted value. When checking whether the input compound is included by the training dataset, this system distinguishes isomers if the input SMILES contains one of @, /, and ¥, otherwise it identifies isomers.

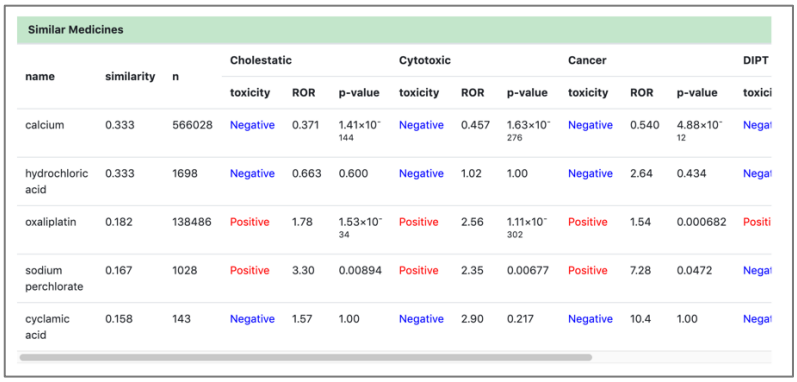
3.2.4. Prediction results of MIE

Below the results of DILI / DIPT prediction, the prediction results of 59 types of MIE follows. The basic meaning of the table and charts are the same as the part of DILI/DIPT, however, there are two models for each MIE so that two predicted values are shown. One model is constructed using criteria of the PubChem activity score $s \geqq 1$ to be regarded as a positive sample. The other model is using criteria $s \geqq 40$.

In the MIE part, there are a few models that could not obtain enough prediction performance. Such model is shown as "Criteria 1 or 40 is unavailable".

3.2.5. Similar medicines

Below the results of MIE prediction, medicines which are similar with the input compounds are shown. These medicines are retrieved from the report of JAPIC AERS.

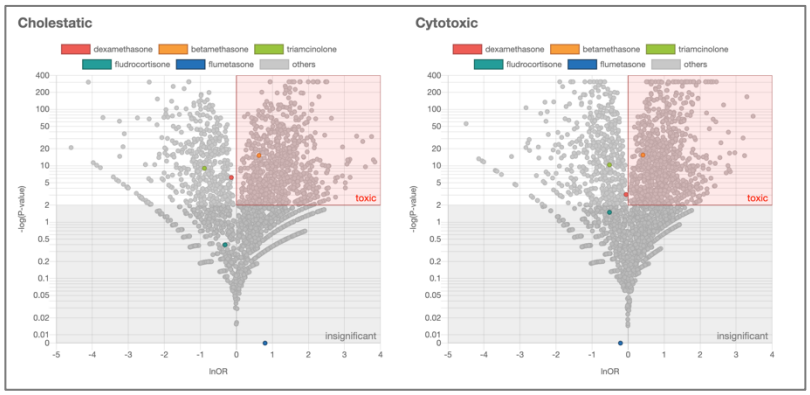


For each similar medicine, the following information is shown.

Name	Description
similarity	Similarity to the input compound （0 ～ 1）
n	Reported count

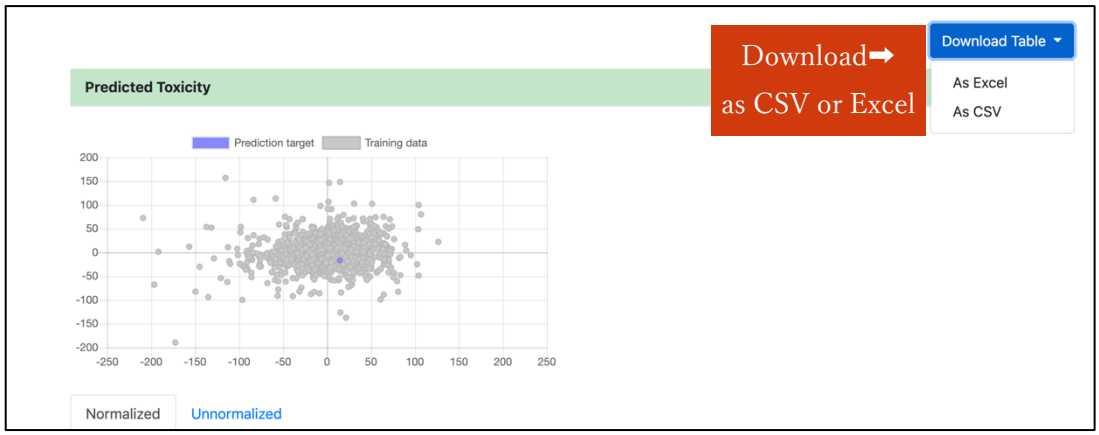
toxicity	Negative, Positive or Insignificant
ROR	Reported Odds Ratio
p-value	Reported significance in p-value
canonical smiles	canonical SMILES (not isomeric)
isomeric smiles	isomeric SMILES

For each DILI and DIPT, a volcano plot is shown as follows. In the volcano plots, a toxic area (toxicity = Positive) is shown as a red area and insignificant area (not enough p-value) is shown as a grey area.



3.2.6. Download prediction results

On the upper right of the page, you can click "Download Table" button to download result of the prediction in CSV or Excel table.

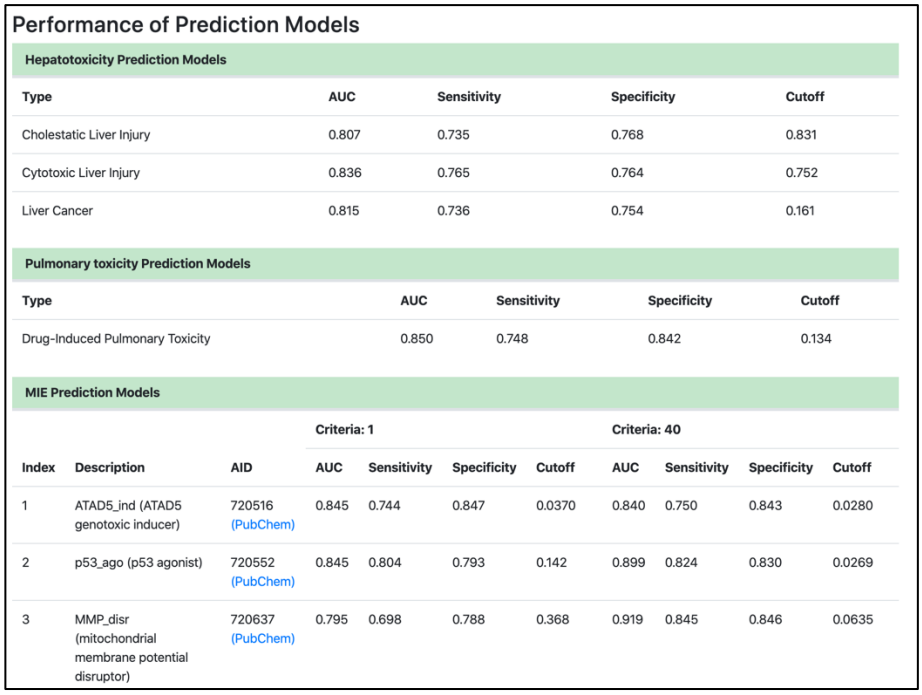


The contents of CSV are as follows.

Column name	Description
SMILES	SMILES of the input compound
<DILI/DIPT name>_normalized	Predicted toxicity for each DILI / DIPT after normalization.
<DILI/DIPT name>_unnormalized	Predicted toxicity for each DILI / DIPT before normalization.
<DILI/DIPT name>_reliability	Prediction reliability for each DILI / DIPT
<MIE name>_normalized_{1, 40}	Predicted value for each MIE after normalization. 1 or 40 stands for criteria.
<MIE name>_unnormalized_{1, 40}	Predicted value for each MIE before normalization. 1 or 40 stands for criteria.
<MIE name>_reliability	Prediction reliability for each MIE.

3.3. About prediction models

If you click the "About Models" menu on the top of each page, you can see the performance of prediction models.



Performance of Prediction Models

Hepatotoxicity Prediction Models

Type	AUC	Sensitivity	Specificity	Cutoff
Cholestatic Liver Injury	0.807	0.735	0.768	0.831
Cytotoxic Liver Injury	0.836	0.765	0.764	0.752
Liver Cancer	0.815	0.736	0.754	0.161

Pulmonary toxicity Prediction Models

Type	AUC	Sensitivity	Specificity	Cutoff
Drug-Induced Pulmonary Toxicity	0.850	0.748	0.842	0.134

MIE Prediction Models

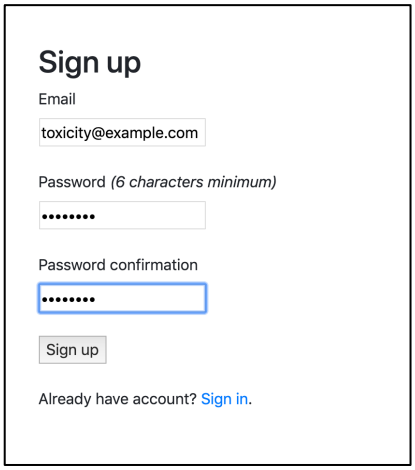
			Criteria: 1				Criteria: 40			
Index	Description	AID	AUC	Sensitivity	Specificity	Cutoff	AUC	Sensitivity	Specificity	Cutoff
1	ATAD5_ind (ATAD5 genotoxic inducer)	720516 (PubChem)	0.845	0.744	0.847	0.0370	0.840	0.750	0.843	0.0280
2	p53_ago (p53 agonist)	720552 (PubChem)	0.845	0.804	0.793	0.142	0.899	0.824	0.830	0.0269
3	MMP_disr (mitochondrial membrane potential disruptor)	720637 (PubChem)	0.795	0.698	0.788	0.368	0.919	0.845	0.846	0.0635

The description of the contents in this page are as the following table.

Name	Description
Type	Name of toxicity (for DILI / DIPT)
AUC	Area Under the Curve of ROC
Sensitivity	The value of sensitivity (TP / (TP + FN))
Specificity	The value of specificity (TN / (TN + FP))
Cutoff	Cutoff value on ROC based on Youden Index
Index	The index of MIE used in this system
Description	The abbreviated name and the detailed name of MIE
AID	Assay ID in PubChem and link to it

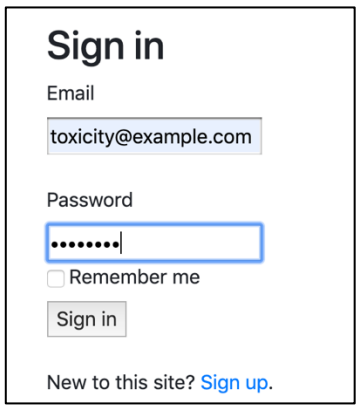
3.4. Sign up / Sign in

This system can be used as an anonymous user. But the history feature (see section 3.2.2) is only available for registered users. To sign up, please click "Sign up" menu on the header menu and input your email address and password. Sign up will be completed immediately after you click "Sign up" button.



After you signed in, you can see the your user name on the right side of the header menu. Please click "Sign out" if you want to sign out.

If you want to sign in again, please click "Sign in" on the header menu and input your email address and password.



Acknowledgements

This system was built using the adverse effect database JAPIC AERS.