

User's Guide for the Chemical Transformation Simulator (CTS), Version 1.0

07/16/2019

Chemical Transformation Simulator:
A Cheminformatics Tool for Predicting
Transformation Pathways and Physicochemical
Properties

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NOTICE

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Purpose

The Chemical Transformation Simulator (CTS) User's Guide is designed to provide the first-time user a complete understanding of how to utilize the CTS tool. The User's Guide may be reviewed from start to finish or by moving directly to a topic of interest through selection of the appropriate topic in the Table of Contents.

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Introduction

The Chemical Transformation Simulator (CTS) provides the calculated physicochemical properties of a target chemical and its transformation products, which are predicted as a function of the reaction system of interest. This is accomplished through the integration of cheminformatics applications for the encoding of process science underlying transformation pathways and computational chemistry tools for the calculation of physicochemical properties.

The CTS consists of three modules, the selection and order of execution of which is based on the user's choice of one of three available workflows as described below.

- **Chemical Editor (CE) Module:** Provides options for chemical entry through SMILES notation, chemical name, CAS #, or drawn structure, as well as speciation of the parent chemical
- **Physicochemical Properties (PCP) Module:** Calculates physicochemical properties for the parent chemical and predicted transformation products based on the executions of multiple physicochemical calculators
- **Reaction Pathway Simulator (RPS) Module:** Generates potential transformation products based on user-specified reaction conditions

Background

A key Agency need identified as a high priority in the Chemical Safety for Sustainability (CSS) National Research Program is for high throughput computational systems to rank chemicals based on hazards and risks. To fully characterize the risks associated with the release of a chemical into the environment, tools are necessary to simulate environmental fate and transport for organic chemicals for which such data are not available. Knowledge of inherent chemical properties (ICP) is essential for the parameterization of environmental fate and transport models. Of the ~85,000 chemicals in the TSCA inventory, it is estimated that high quality measured ICP data are available for less than 2% of these chemicals. Additionally, 20 to 30 new chemicals a month are being assessed through the Office of Pollution Prevention and Toxics (OPPT) Pre-Manufacturing Notification (PMN) process. This ever-growing data gap must be addressed through the development of a high throughput computational system for calculating the ICP necessary for the parameterization of environmental fate models used to estimate environmental concentrations of both the parent chemical and predicted transformation products as a function of environmental conditions.

The key components of the CTS are the Physicochemical Properties module (PCP) and the Reaction Pathway Simulator module (RPS). The PCP is based on a consensus approach that allows the user to compare output generated by several calculators that take different approaches to calculating specific physicochemical properties. These calculators include (1) EPI Suite, which uses a fragment-based approach, (2) TEST (Toxicity Estimation Software Tool), which uses Quantitative Structure Activity Relationship (QSAR)-based approaches, (3) ChemAxon plug-in calculators, which use an atom-based fragment approach, and (4) OPERA (OPEN structure-activity/property Relationship App), which uses a weighted k-nearest neighbor approach to construct QSAR and Quantitative Structure Property Relationship (QSPR) models. The output derived from these calculators will enable the user to compare the calculated data with measured data in readily accessible web-based databases.

The output of the RPS is based on the selection and execution of reaction libraries that represent one-step reactions for transformation (e.g., abiotic reduction and hydrolysis) of reactive functional groups. These one-step reactions represent viable transformation pathways based on the identification and subsequent transformation of reactive functional groups. A reaction library for human phase I metabolism developed by ChemAxon is also available through the CTS. The development of reaction libraries allows us to “encode” the known process science published (current and future) in the peer-reviewed literature. The encoding of process science is accomplished using Chemical Terms Language and Smart Reaction strings through cheminformatics applications. The execution of these reaction libraries provides dominant transformation pathways and products for the chemical of interest as a function of environmental conditions.

Using the CTS Software

Restrictions

The CTS is designed to predict transformation pathways and calculate physicochemical properties for organic chemicals. The CTS is designed for users with expertise regarding the environmental processes controlling the degradation of organic chemicals and the use of physicochemical properties in environmental fate modeling. Currently, organometallics, non-dissociating salts of organic chemicals, and polymers are not recognized by the CTS. To provide CTS users with a rich user experience we take advantage of features specified in the HTML 5 standards. Internet Explorer does not fully implement support for HTML 5 standards. As a result, CTS functionality will be limited when using the Internet Explorer web browser. We recommend using the latest version of Google Chrome or Mozilla Firefox.

Accessing the CTS

Currently users have access to the CTS through a password system. The CTS can be accessed through <https://qed.epacdx.net/cts/>, which provides the models currently available on the web Quantitative Exposure Domain (QED) as shown in the screen shot below.

Quantitative Exposure Domain

Q.E.D.

[public](#)

[epa internal](#)

CSS Apps

[cts](#)

[pram](#)

SHC Apps

SSWR Apps

[hms](#)

Docs

[api documentation](#)

[source code](#)

[wiki](#)

Environmental Models and Services

Chemical Transformation Simulator

The Chemical Transformation Simulator (CTS) provides the calculated physicochemical properties of the parent chemical and transformation products, which are predicted as a function of the reaction system of interest. This is accomplished through the integration of cheminformatics applications for the encoding of process science underlying transformation pathways, computational chemistry tools for the calculation of physicochemical properties, and software technologies that provide access to on-line databases for environmental descriptors required for estimating environmental concentrations.

Hydrological Micro Services

Hydrological Micro Services (HMS) provides component and model data services relates to hydrology (e.g., evapotranspiration, precipitation, surface runoff, subsurface flow, soil moisture, temperature) and water quality (e.g., chemistry, eutrophication, mercury, microbes, nutrients, pH levels, sediment and temperature).

pram: Pesticide risk assessment models

Pram is a cloud-based web application platform that includes a variety of aquatic, terrestrial and atmospheric deposition fate and transport models used by the EPA for the ecological risk assessment of pesticides. The science models in the übertool provide predictions concerning chemical concentrations in environmental media, exposure doses, tissue residues and ultimately predictions of effects. These predictions are relevant for a number of ecological species under regulations that the EPA is responsible for, including the registration of pesticides and the protection of endangered species.

CTS Homepage: The home page of the CTS is accessed by clicking on the CTS link. The home page provides access to the CTS through the selection of one of three CTS workflows and general information concerning the major modules of the CTS, the physicochemical calculators and reaction libraries as shown in the screen shot below.

CTS: Chemical Transformation Simulator

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What is CTS?

The Chemical Transformation Simulator (CTS) is a web-based tool for predicting environmental and biological transformation pathways and physicochemical properties of organic chemicals.

CTS Workflows

Three workflows have been implemented in CTS to help users predict how organic chemicals are partitioned, transformed and metabolized in environmental and biological systems. More information about the individual workflows and modules is available under the tabs in the navigation panel.

Calculate Chemical Speciation Workflow: Calculates the speciation (i.e., ionization as a function of pH, tautomer distribution, and possible stereoisomers) of the entered chemical.

Calculate Physicochemical Properties Workflow: Calculates physicochemical properties for the entered chemical using four stand-alone calculators: EPI Suite, ChemAxon, TEST, and OPERA.

Generate Transformation Products Workflow: Generates transformation products of the entered chemical based on user-specified conditions and reaction libraries. Once transformation products are generated, physicochemical properties for one or more parent or product chemicals can be calculated within the workflow.

CTS Modules Overview

Chemical Editor (CE): CTS's Chemical Editor (CE) appears at the beginning of all workflows and allows users to enter chemicals by their name, Chemical Abstracts Service Registry Number (CAS#), Simplified Molecular-Input Line-Entry System (SMILES) string, or by drawing the chemical's structure. ChemAxon's Marvin and JChem applications and EPA's CompTox Chemistry Dashboard (<https://comptox.epa.gov/dashboard>) are used to generate a standardized SMILES string, preferred common name, IUPAC name, chemical formula, relevant CAS numbers, average and monoisotopic masses, and the DTXSID (unique substance identifier assigned by EPA's National Center for Computational Toxicology (NCCT)) for the selected chemical.

Chemical Speciation: CTS's Chemical Speciation (CS) workflow uses ChemAxon's Plugin Calculators to generate:

- The speciation of a chemical as a function of pH;
- The ionization constant(s);
- The dominant tautomer distribution; and
- Structures for all possible isomers.

Physicochemical Properties (PCP) Module: CTS's Physicochemical Properties Module calculates physicochemical properties for the parent chemical and predicted transformation products based on the findings of multiple physicochemical calculators. The PCP is based on a consensus approach that allows users to compare output from multiple calculators that use different approaches to calculate specific physicochemical properties.

The calculators that PPC is currently accessing include:

1. EPI Suite, which uses a QSAR approach with either fragment counts or properties as descriptors;
2. Toxicity Estimation Software Tool (TEST), which implements several approaches, including fragment-based QSARs, hierarchical clustering with structural similarity based on a variety of 2-D physicochemical descriptors, and nearest neighbor;
3. ChemAxon plug-in calculators, which are based on QSARs with either atom or fragment counts as descriptors; and
4. OPEn structure activity/property Relationship App (OPERA), which uses a weighted k-nearest neighbor approach to construct QSAR/QSPR models based on 2-D physicochemical descriptors.

Users also have the option to request measured data that is available in the EPI Suite PHYSPROP physicochemical property database. In addition, the geometric mean of the predicted values (not including any measured data or ionization constants) for each selected property from the selected calculators will be automatically calculated and displayed in the table when predicted values are requested. Further information on the calculation of the geometric mean is provided in the Physicochemical Properties Module section of this document.

Reaction Pathway Simulator (RPS): CTS's Reaction Pathway Simulator (RPS) generates potential transformation products based on user-specified reaction conditions. The output of the RPS is based on the selection and execution of reaction libraries that represent reaction schemes for the transformation of reactive functional groups that are susceptible to processes such as reduction and hydrolysis. These reaction schemes denote viable transformation pathways based on the identification and transformation of the reactive functional groups. A rank is assigned to each one of the reaction schemes based on available experimental data. The rank is essentially a relative reaction rate, defined on a scale of one to seven, with seven being assigned to the fastest reaction schemes. The rank of each scheme is used to calculate an approximate percentage production of each potential transformation product.

In Metabolizer, an algorithm has been implemented to approximate a percent production and accumulation for products of each reaction scheme. In the Metabolizer algorithm, the unitless “formation” value for scheme i (f_i) is defined as the number 7 raised to the power of the rank:

$$f_i \stackrel{\text{def}}{=} 7^{\text{Rank}_i}$$

The “formation” values are analogous to rate constants, and the “production” (in %) of the product(s) generated by scheme i is calculated according to the following equation:

$$\% P_i = \frac{100 f_i}{\sum_{j=1}^N f_j}$$

where N is the total number of transformation schemes in the current generation. The “accumulation” of the product formed by scheme i is then calculated as the difference between f_i and the summation of the formation values for all M schemes that may transform the product in the next generation, normalized by the summation of the formation values for all transformation schemes in the current generation:

$$\% A_i = \frac{100(f_i - \sum_{l=1}^M f_l)}{\sum_{j=1}^N f_j}$$

A more detailed description of the production and accumulation calculations is provided in the online documentation for the CTS Reaction Libraries.

Developing reaction libraries allows scientists to “encode” the known process science published – current and future – in the peer-reviewed literature. Encoding process science is accomplished by using Chemical Terms Language and cheminformatics applications. Reaction libraries have been developed for the environmental transformation processes of abiotic hydrolysis and abiotic reduction. A reaction library for human phase I metabolism that was developed by ChemAxon is also available through the RPS.

Executing these reaction libraries provides dominant transformation pathways and products for the chemical of interest as a function of environmental conditions. Users also have the option to

execute the PCP for the calculation of physicochemical properties for the parent chemical and transformation products.

Links to the process science supporting the currently available reaction libraries are also available. For example, clicking on the Reaction Libraries tab, followed by clicking “Click here to download the abiotic hydrolysis library” as shown in the screen shot below.

Abiotic Hydrolysis Reaction Library

Version 1.6 of the Abiotic Hydrolysis Reaction Library contains 25 reaction schemes:

- [Halogenated Aliphatics: Nucleophilic Substitution](#)
 - Scheme A: C-X with no other adjacent halogens
 - Scheme B: C-X with vicinal halogen atoms
 - Scheme C: C-X with geminal halogen atoms
- [Halogenated Aliphatics: Elimination](#)
- [Epoxide Hydrolysis](#)
- [Organophosphorus Ester Hydrolysis 1 \(Base-Catalyzed\)](#)
- [Organophosphorus Ester Hydrolysis 2 \(Neutral or Acid-Catalyzed\)](#)
- [Carboxylic Acid Ester Hydrolysis](#)
- [Lactone Hydrolysis](#)
- [Carbonate Hydrolysis](#)
- [Cyclic Carbonate Hydrolysis](#)
- [Anhydride Hydrolysis](#)
- [Cyclic Anhydride Hydrolysis](#)
- [Amide Hydrolysis](#)
- [Lactam Hydrolysis](#)
- [Carbamate Hydrolysis](#)
- [Urea Hydrolysis](#)
- [Cyclic Urea Hydrolysis](#)
- [Sulfonylurea Hydrolysis](#)
- [Thiocarbamate Hydrolysis](#)
- [Nitrile Hydrolysis](#)
- [N-S Cleavage](#)
- [Imide Hydrolysis](#)
- [Acid Halide Hydrolysis](#)
- [Dehydration of Geminal Diols](#)

Selection of one of the transformation pathways provides the reaction scheme, and documented examples with references. The following illustrates this information for Epoxide Hydrolysis:

EXAMPLES:

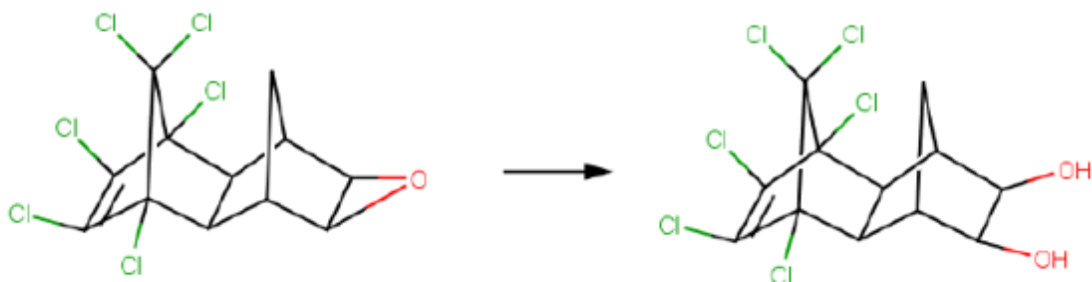
- 1,2-Epoxycyclohexane (McMurry, 2011)



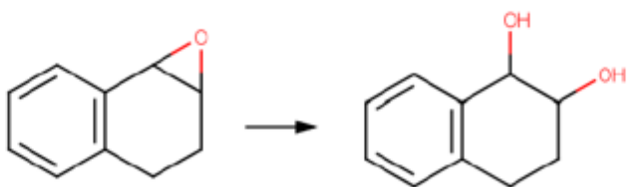
- Epichlorohydrin (Gaca *et al*, 2011)



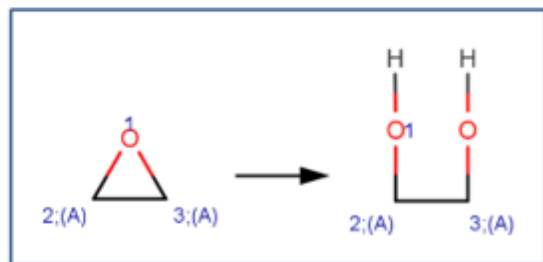
- Endrin (Larsen and Weber, 1994; U.S. EPA, 1992)



- 1,2-Epoxy-1,2,3,4-tetrahydronaphthalene (Becker *et al*, 1979)



SCHEME:



Execution of the CTS

The CTS is executed by selecting one of three available workflows (see descriptions below) and by entering a single chemical or by batch mode. The process for entering a single chemical or by batch, as described below, is identical for each of the workflows.

Single Chemical Entry

For single chemical entry, the “Run single chemical” tab is selected below the workflow of interest in the left-hand frame. The Chemical Editor appears where there is the option to either enter a SMILES String, name, or Chemistry Abstracts Service (CAS) # in the Lookup Chemical box, or to draw a chemical structure using the Chemical Editor (see screen shot below). For either case, the appropriate box must be clicked after providing the required information. Details concerning the use of the chemical editor can be found at <https://docs.chemaxon.com/display/docs/MarvinSketch>.

The screenshot displays the CTS: Chemical Transformation Simulator interface. The main heading is "Calculate Chemical Speciation". Below this, there are two primary options: "Lookup Chemical" and "Draw Chemical Structure".

Lookup Chemical: This section includes a text input field and a button labeled "Enter a SMILES, Name, or CAS# and Click Here".

Draw Chemical Structure: This section includes a button labeled "Draw a chemical structure and Click Here" and a window for the Marvin JS chemical editor. The editor window shows a toolbar with various drawing tools and a central canvas with the Marvin JS logo and ChemAxon branding. A vertical menu on the right side of the editor lists chemical elements: H, C, N, O, S, F, P, Cl, Br, I, and A.

Left-hand navigation menu:

- About**
 - CTS Home
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- Execute CTS Workflows**
 - Calculate Chemical Speciation**
 - Run single chemical
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Batch Chemical Entry

For batch chemical entry, the “Run batch file” tab is selected below the workflow of interest in the left-side frame. By clicking on the sample batch input link, the example batch file, shown below in the screen shot, is opened or downloaded. The chemicals are entered as a single column of SMILES strings. The default value is currently set to a maximum of 10 chemicals.

Sample batch input:

```
C1=CC=CC=C1
CC(=O)OC1=CC=CC=C1C(O)=O
OC1=CC=CC=C1
OC(=O)CC(O)(CC(O)=O)C(O)=O
[O-][N+](=O)C1=CC=C(C=C1)[N+](=O)[O-]=O
```

The screenshot displays the CTS: Chemical Transformation Simulator interface. On the left is a navigation sidebar with sections: 'About' (CTS Home, About CTS), 'Execute CTS Workflows' (Calculate Chemical Speciation, Run single chemical, Run batch file), 'Calculate Physicochemical Properties', 'Generate Transformation Products', and 'Documentation' (Download CTS User's Guide (PDF), CTS Modules, Physicochemical Calculators, Reaction Libraries, API Documentation, Manuscripts, Version History, Help). The main content area is titled 'Calculate Chemical Speciation Batch Run' and contains a list of instructions: 'Upload a text file of SMILES strings organized into a single column (View/download sample batch input file):' and 'File to upload: Choose File No file chosen'.

Execution of the CTS Workflows

The user executes the CTS through the selection of one of three available workflows:

- Calculate Chemical Speciation
- Calculate Physicochemical Properties
- Generate Transformation Products

Calculate Chemical Speciation Workflow

Selection of the Calculate Chemical Speciation Workflow provides this page illustrating the workflow overview as illustrated below. ChemAxon calculator plugins are executed for the calculation of chemical speciation.

CTS: Chemical Transformation Simulator

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Execute CTS Workflows

- Calculate Chemical Speciation**
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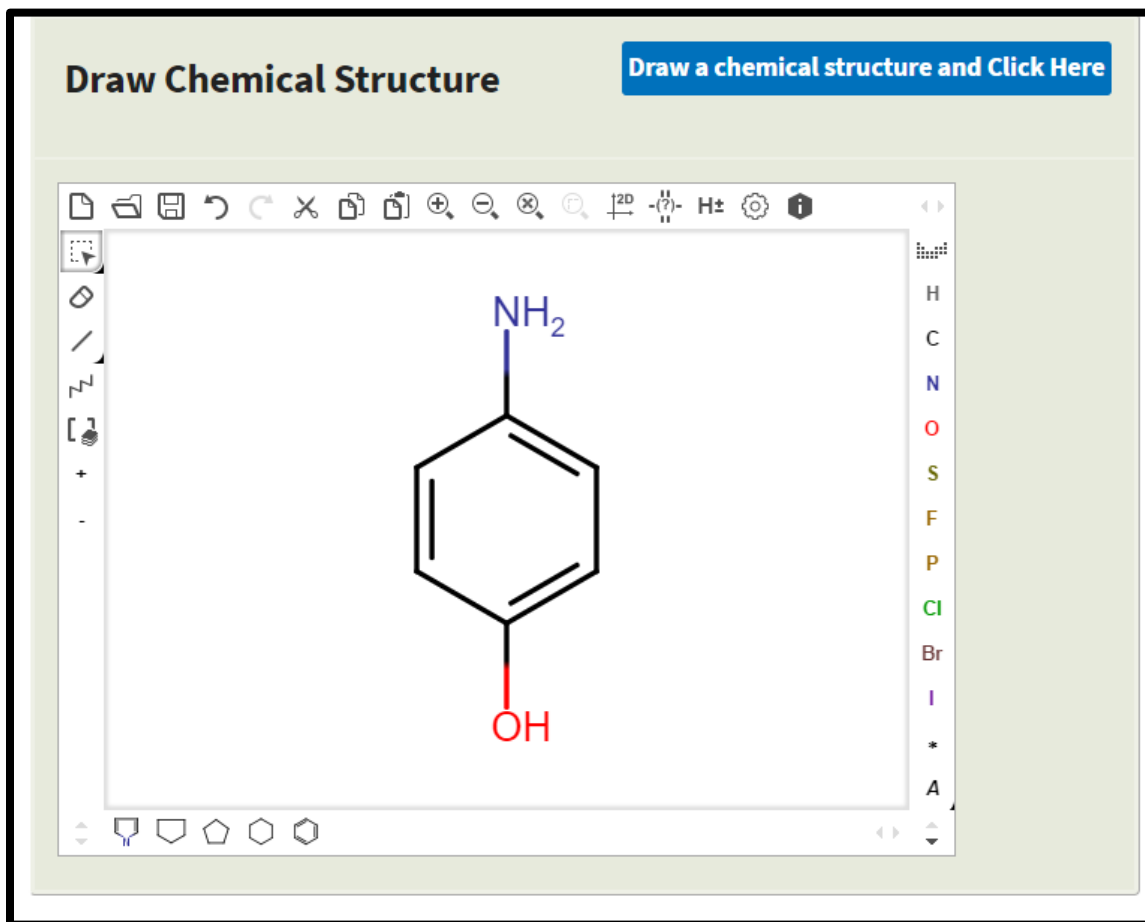
- Download CTS User's Guide (PDF)
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Calculate Chemical Speciation Overview

This workflow allows you to enter an individual chemical through the Chemical Editor (see below). Based on the selection of the available options for structure analysis, you will be able to generate structure information including ionization constants (pKa values), the dominant forms of ionized species and tautomers, as well as structures for possible stereoisomers.

```
graph LR; CE[Chemical Editor] --> P[Protonation: - pKa calculation - Microspecies distribution]; CE --> TD[Tautomer Distribution]; CE --> SG[Stereoisomer Generation];
```

Clicking on the “Run single chemical” link takes the user to the Chemical Editor. For the following example, 4-aminophenol was entered into the Chemical Editor as shown in the screen shot below.



After clicking the Next button at the bottom of the Chemical Editor or the Chemical Speciation link at the top of the workflow frame, select from three available options for calculating chemical speciation as shown in the screen shot below.

Calculate Chemical Speciation

Chemical Editor | Chemical Speciation

Check one or more calculation methods to run, then hit submit below

Calculate Ionization Constants (pKa) Parameters	
Number of decimals for pKa:	<input type="text" value="2"/>
pH Lower Limit:	<input type="text" value="0"/>
pH Upper Limit:	<input type="text" value="14"/>
pH Step Size:	<input type="text" value="0.2"/>
Generate Major Microspecies at pH:	<input type="text" value="7.0"/>
Isoelectric Point (pI) pH Step Size for Charge Distribution:	<input type="text" value="0.5"/>

Calculate Dominant Tautomer Distribution	
Maximum Number of Structures:	<input type="text" value="100"/>
at pH:	<input type="text" value="7.0"/>

Calculate Stereoisomers	
Maximum Number of Structures:	<input type="text" value="100"/>

Select any combination of the calculators; use the provided default values or change the default values required by the user. The following parameters can be adjusted:

- **Calculate Ionization Constants**

- Number of decimals: Number of decimal places calculated for acidic and basic pK_a values
- pH Lower limit: Specifies the lower end of the pH range for which the microspecies will be generated
- pH Upper limit: Specifies the upper end of the pH range for which the microspecies will be generated
- Generate Major Microspecies at pH: Generates the Major Microspecies at the specified pH.
- pH step size: Specifies the pH step size for the X-Axis of the plot illustrating the distribution of the microspecies as a function of pH
- Isoelectric Point (pI) pH Step Size for Charge Distribution: Specifies the pH step size for the X-Axis of the plot illustrating the Isoelectric Point and charge distribution as a function of pH

- **Calculate Dominant Tautomer Distribution**

- Maximum Number of Structures: Specifies the maximum number of structures that will be generated.
- At pH: Specifies the pH at which the dominant tautomer distribution will be calculated

- **Calculate Stereoisomers**

- Maximum Number of Structures: Specifies the maximum number of structures that will be generated.

The user also has the option of running a batch file. By clicking on the “Run batch file link”, the following screen appears. The user has the option to view or download a sample batch input file or enter a file by clicking on the Choose File button.

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Calculate Chemical Speciation Batch Run

- Upload a text file of SMILES strings organized into a single column (View/download sample batch input file):
- File to upload: No file chosen

Calculate Ionization Constants

Once the calculator(s) has been chosen and the appropriate parameters entered, click the Submit button to view the results. The calculator for ionization constants has been chosen for this demonstration as shown in the screen shot below.

Inputs: The molecular information and ionization parameters provided by the user.

Calculate Chemical Speciation

Chemical Editor | Chemical Speciation

Check one or more calculation methods to run, then hit submit below

Calculate Ionization Constants (pKa) Parameters

Number of decimals for pKa:	2
pH Lower Limit:	0
pH Upper Limit:	14
pH Step Size:	0.2
Generate Major Microspecies at pH:	7.0
Isoelectric Point (pI)	0.5
pH Step Size for Charge Distribution:	0.5

The results of the ionization constant calculation are illustrated in the screen shots below:

- **pKa Calculations:** Provides the chemical structure entered, the generated microspecies, and the distribution of microspecies as a function of pH over the pH range specified. Results are color coded.
- **Isoelectric Point:** The isoelectric point is provided as well as a graph illustrating the charge on the chemical as a function of pH.
- **Major Microspecies:** The dominant microspecies formed at the pH selected.

- Results

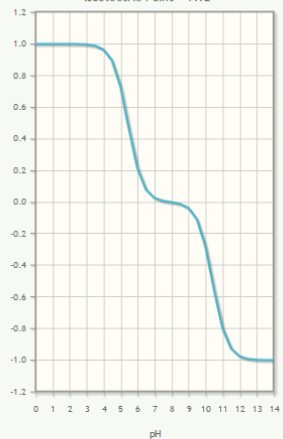
- pKa

Basic pKa Value(s): [5.43]

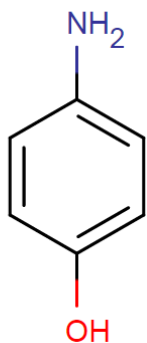
Acidic pKa Value(s): [10.4]

- Isoelectric Point

Isoelectric Point = 7.92

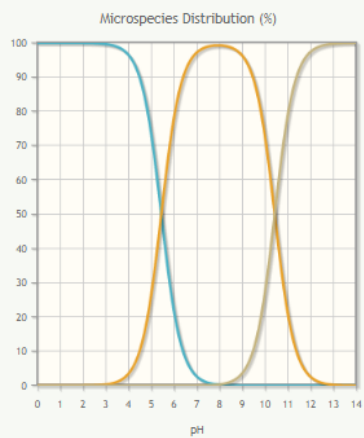
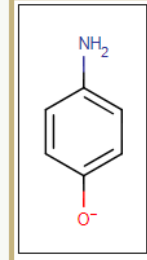
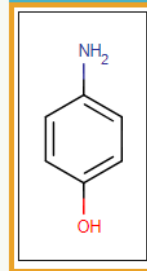
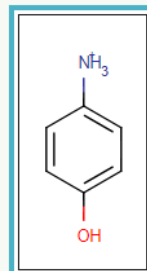
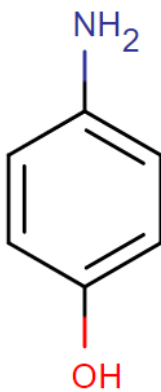


- Major Microspecies at pH: 7.0



Microspecies

Parent



Calculate Dominant Tautomer Distribution

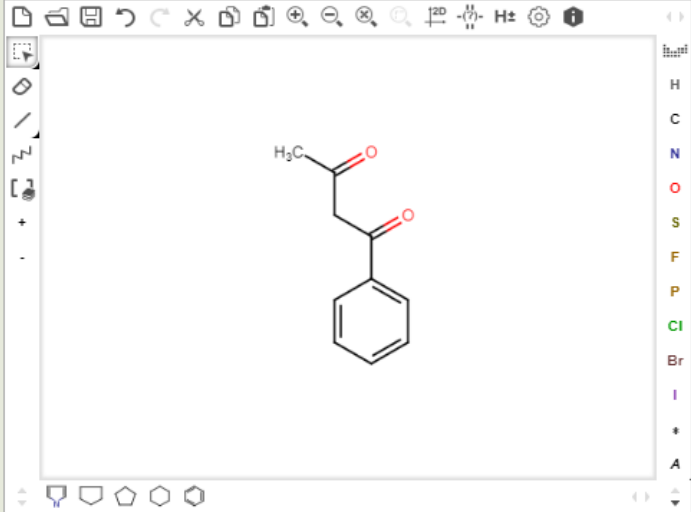
The CTS uses ChemAxon's tautomerization engine for the calculation of the dominant tautomer distribution. For this demonstration, 1-phenylbutane-1,3-dione has been entered into the Chemical Editor as shown in the screen shot below.

Lookup Chemical

Enter a SMILES, Name, or CAS# and Click Here

Draw Chemical Structure

Draw a chemical structure and Click Here



The image shows a chemical structure editor window. The central canvas displays the chemical structure of 1-phenylbutane-1,3-dione, which consists of a benzene ring attached to a four-carbon chain. The first carbon of the chain is part of a methyl ketone group (CH₃-C(=O)-), and the third carbon is part of another ketone group (-C(=O)-). The structure is drawn in a skeletal format with red oxygen atoms. The editor includes a toolbar at the top with various drawing tools and a vertical element palette on the right listing elements like H, C, N, O, S, F, P, Cl, Br, I, and A.

Results

Entered Chemical	<input type="text" value="1-phenylbutane-1,3-dione"/>
Initial SMILES	<input type="text" value="CC(=O)CC(=O)C1=CC=CC=C1"/>
Standardized SMILES	<input type="text" value="CC(=O)CC(=O)C1=CC=CC=C1"/>

Clicking the Next button brings up the Calculate Chemical Speciation Workflow Inputs page. After selecting the Calculate Dominant Tautomer Distribution option, enter a limit for the number of possible tautomers and the pH value for which the distribution will be calculated. The default values are pH 7.0 and a limit of 100 tautomers as shown in the screen shot below.

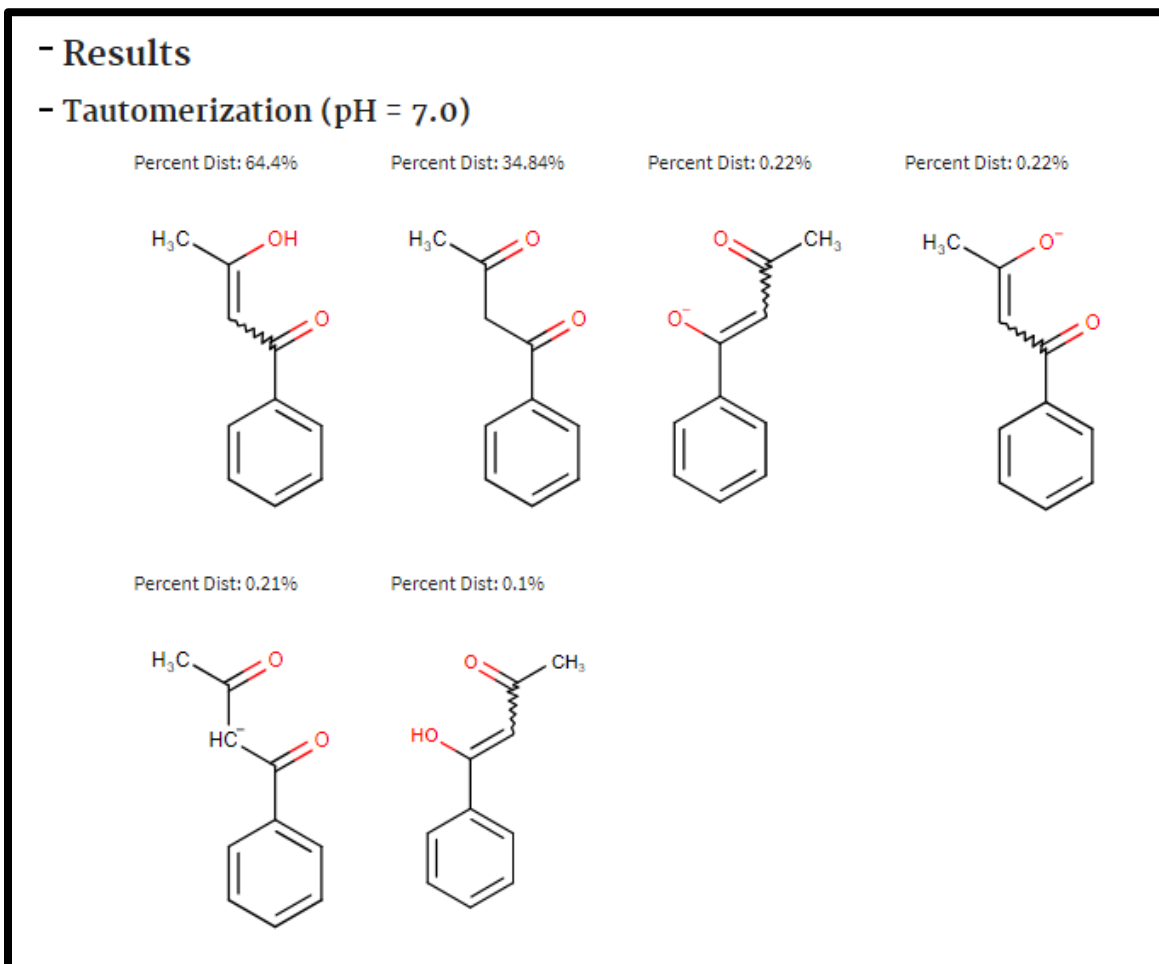
<input type="checkbox"/> Calculate Ionization Constants (pKa) Parameters	
Number of decimals for pKa:	<input type="text" value="2"/>
pH Lower Limit:	<input type="text" value="0"/>
pH Upper Limit:	<input type="text" value="14"/>
pH Step Size:	<input type="text" value="0.2"/>
Generate Major Microspecies at pH:	<input type="text" value="7.0"/>
Isoelectric Point (pI) pH Step Size for Charge Distribution:	<input type="text" value="0.5"/>

<input checked="" type="checkbox"/> Calculate Dominant Tautomer Distribution	
Maximum Number of Structures:	<input type="text" value="100"/>
at pH:	<input type="text" value="7.0"/>

<input type="checkbox"/> Calculate Stereoisomers	
Maximum Number of Structures:	<input type="text" value="100"/>

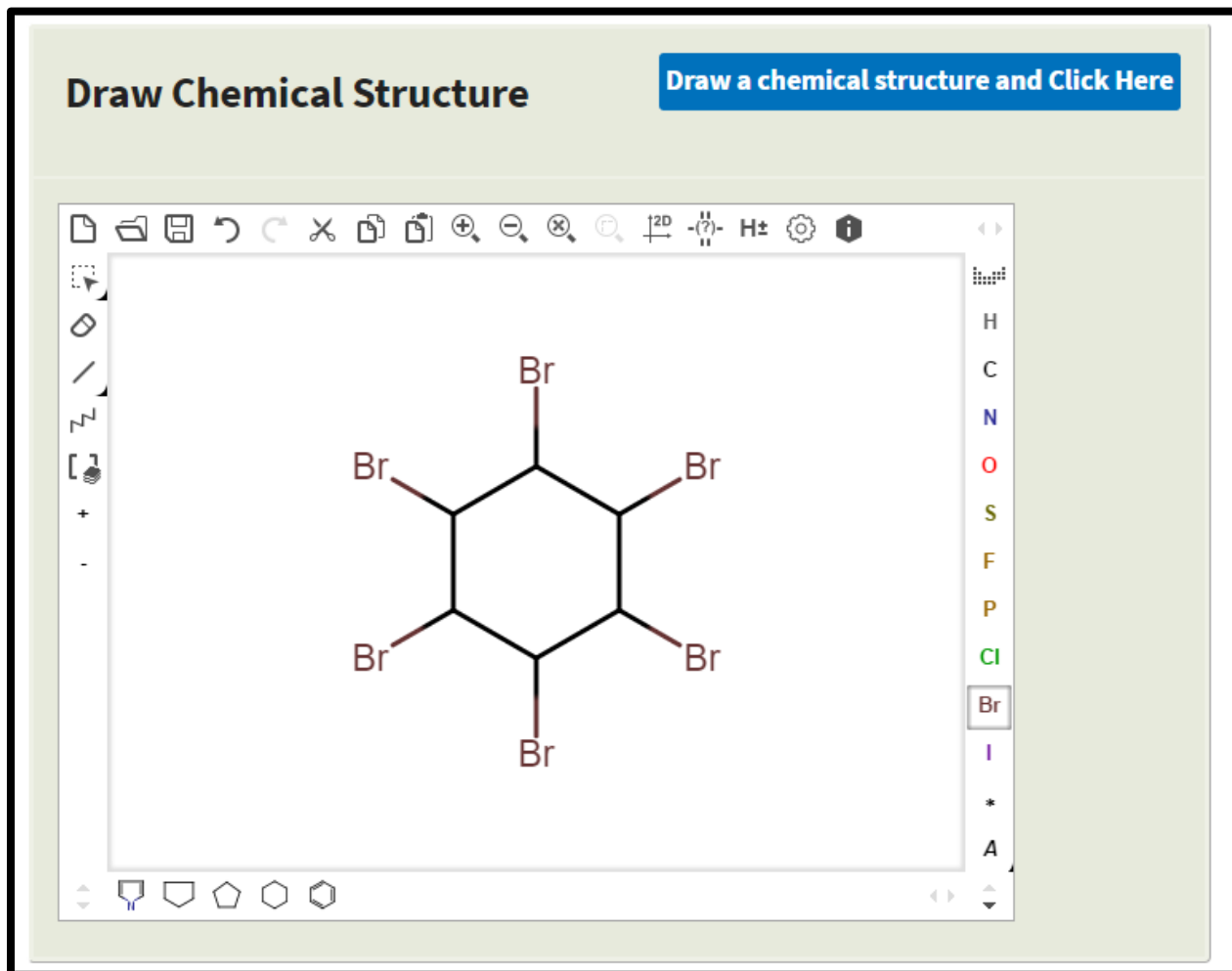
Click on the Submit button to view the output page for the tautomerization distribution based on the user-defined values.

The Output screen shows the User Inputs (see screen shot above) as well as the tautomer distribution for the chemical of interest (see screen shot below). The individual structures can be enlarged by placing the cursor on top of the structure. The molecular information including the formula, IUPAC name, mass and SMILES string is also provided.



Calculate Stereoisomers

For this demonstration, 1,2,3,4,5,6-hexabromocyclohexane has been entered into the Chemical Editor as shown in the screen shot below.



<input type="checkbox"/> Calculate Ionization Constants (pKa) Parameters	
Number of decimals for pKa:	<input type="text" value="2"/>
pH Lower Limit:	<input type="text" value="0"/>
pH Upper Limit:	<input type="text" value="14"/>
pH Step Size:	<input type="text" value="0.2"/>
Generate Major Microspecies at pH:	<input type="text" value="7.0"/>
Isoelectric Point (pI) pH Step Size for Charge Distribution:	<input type="text" value="0.5"/>

<input type="checkbox"/> Calculate Dominant Tautomer Distribution	
Maximum Number of Structures:	<input type="text" value="100"/>
at pH:	<input type="text" value="7.0"/>

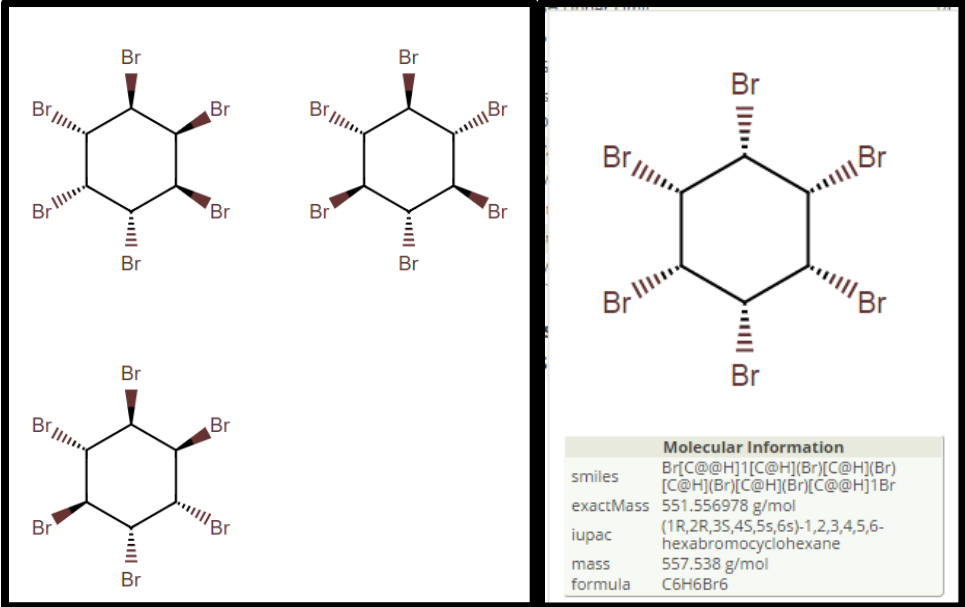
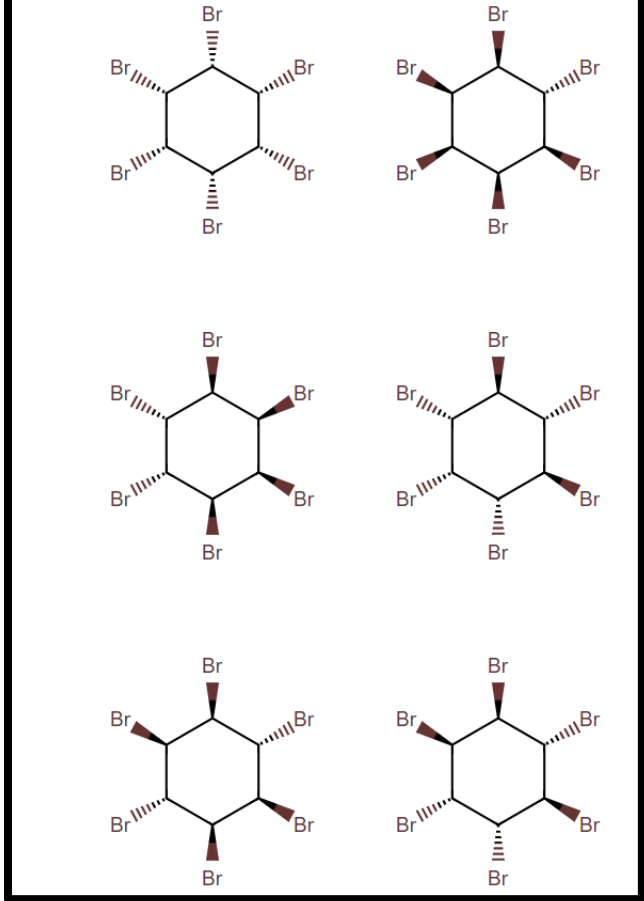
<input checked="" type="checkbox"/> Calculate Stereoisomers	
Maximum Number of Structures:	<input type="text" value="100"/>

After selecting the Calculate Stereoisomers option, enter a limit for the maximum number of possible stereoisomers. The default value is 100 stereoisomers as shown in the screen shot above.

Clicking on the Next button provides the results of the calculation, which illustrate that 1,2,3,4,5,6-hexabromocyclohexane can exist as nine different stereo isomers as shown in the screen shot below. The individual structures can be enlarged by placing the cursor over the structure. The molecular information including the formula, IUPAC name, mass and SMILES string is also provided.

Results

Stereoisomers (9)



Calculate Physicochemical Properties Workflow

Selection of the Calculate Physicochemical Properties Workflow provides the screen shot below illustrating the workflow overview. Click on the “Run single chemical” link to submit a single chemical for processing, or click on the “Run batch file” link to submit a batch file.

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Calculate Physicochemical Properties Overview

This workflow allows you to enter an individual chemical through the Chemical Editor (see below) or through batch mode (select Batch tab). Based on your selection of the available physicochemical calculators and physicochemical properties, you will be able to generate calculated physicochemical properties of interest.

```
graph TD; A[Chemical Editor] --> B[Select Physicochemical Calculators]; B --> C[Select Physicochemical Properties]; C --> D[Physicochemical Properties Calculator];
```

For this demonstration, 1-methoxy-2,4-dinitrobenzene has been entered into the Chemical Editor. The results are shown in the screen shots below. Select the Next button to choose the physicochemical calculators and physicochemical properties of interest.

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Calculate Physicochemical Properties

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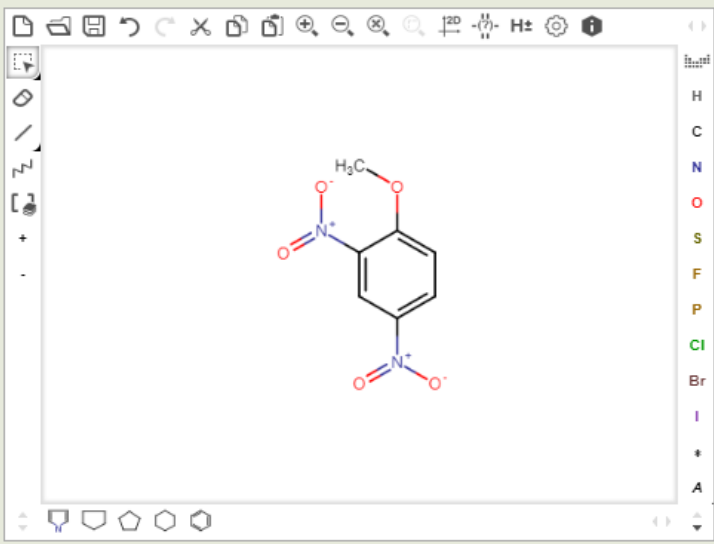
Enter a SMILES, Name, or CAS#, or draw a chemical, then click the button located in the top right of the chosen method to get results. Click the "next" button below or click the "Physicochemical Calculators" link above to continue through the workflow.

Lookup Chemical

[Enter a SMILES, Name, or CAS# and Click Here](#)

Draw Chemical Structure

[Draw a chemical structure and Click Here](#)



Results

Entered Chemical	1-methoxy-2,4-dinitrobenzene
Initial SMILES	<chem>COC1=CC=C(C=C1[N+](=O)[O-])[N+](=O)[O-]</chem>
Standardized SMILES	<chem>COC1=CC=C(C=C1[N+](=O)[O-])[N+](=O)[O-]</chem>
Preferred Name	2,4-Dinitroanisole
IUPAC	1-methoxy-2,4-dinitrobenzene
Formula	C7H6N2O5
Preferred CAS	119-27-7
Associated CAS	119-27-7
DTXSID	DTXSID9041366
Average Mass (g/mol)	198.134
Monoisotopic Mass (g/mol)	198.027671301

Clear

Next

Use the Calculate Physicochemical Properties Workflow Inputs screen to select physicochemical properties and the physicochemical calculators of interest as shown in the screen shot below. Selection of the All button for the physicochemical properties selects all properties no matter which calculators are chosen, although only the available properties from each calculator will be calculated. See Table 1 for a summary of the calculators and calculation methods used in the Physicochemical Properties Calculator.

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Calculate Physicochemical Properties

Chemical Editor | Physicochemical Calculators

Check chemical properties and which calculators to compute them, then hit submit

	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
	ChemAxon	EPI Suite	TEST	OPERA	Geometric Mean	Measured
<input checked="" type="checkbox"/> All						
Neutral Species Inputs:						
<input checked="" type="checkbox"/> Melting Point (°C)						
<input checked="" type="checkbox"/> Boiling Point (°C)						
<input checked="" type="checkbox"/> Water Solubility (mg/L)						
<input checked="" type="checkbox"/> Vapor Pressure (mmHg)						
<input checked="" type="checkbox"/> Ionization Constant						
<input checked="" type="checkbox"/> Henry's Law Constant (atm·m ³ /mol)						
<input checked="" type="checkbox"/> Octanol/Water Partition Coefficient (log)						
<input checked="" type="checkbox"/> Organic Carbon Partition Coefficient (log(L/kg))						
<input checked="" type="checkbox"/> Bioconcentration Factor (log(L/kg))						
<input checked="" type="checkbox"/> Bioaccumulation Factor (log(L/kg))						
pH-Dependent Inputs						
at pH: <input style="width: 50px;" type="text" value="7.0"/>						
<input checked="" type="checkbox"/> Octanol/Water Distribution Coefficient (log)						
<input checked="" type="checkbox"/> Water Solubility (mg/L)						
	Available	Unavailable				

Clear
Back
Submit

Application or Website	Version	Model	Property	Calculation Method	References
ChemAxon Plugin Calculators	16.10.31.0	KLOP	Kow, Dow	Group Contribution: MLR with fragment counts as descriptors	Klopman et al. (1994)
		VG	Kow, Dow	Group Contribution: MLR with fragment counts as descriptors	Viswanadhan et al. (1989)
		PHYS	Kow, Dow	Group Contribution: MLR with fragment counts as descriptors	Based on Viswanadhan et al. (1989) with PHYSPROP as training set
		Solubility Predictor	WS	Group Contribution: MLR with atom counts as descriptors	Hou et al. (2004)
		pKa Predictor	pKa	Ionization site-specific regression equations	Szegezdi and Csizmadia (2004, 2007)
EPI Suite	4.11	KOWWIN™	Kow	Group Contribution: MLR with fragment counts as descriptors	Meylan and Howard (1995)
		WATERNT	WS	Group Contribution: MLR with fragment counts as descriptors	US EPA (2012)
		WSKOW	WS	MLR with log Kow, MP and MW as descriptors	Meylan et al. (1996); US EPA (2012)
		KOCWIN	Koc	MCI-based QSAR; MLR with log Kow as descriptor	Meylan et al. (1992)
		MPBPVP	MP, BP, VP	Group Contribution: MLR with fragment counts as descriptors for MP and BP; VP from nonlinear function of BP	US EPA (2012)
		HENRYWIN	HLC	Bond Contribution: MLR with bond counts as descriptors	US EPA (2012)
		BCFBAF™	BCF and BAF	MLR with log Kow as descriptor; Arnot-Gobas method using upper trophic values	US EPA (2012)
T.E.S.T.	4.2	FDA	MP, BP, WS, VP, BCF	Hierarchical Clustering with similar chemicals	Contrera et al. (2003); Martin et al. (2008)
		Group Contribution	MP, BP, WS, VP, BCF	Group Contribution: MLR with fragment counts as descriptors	Martin and Young (2001)
		Hierarchical Clustering	MP, BP, WS, VP, BCF	Hierarchical Clustering	Martin et al. (2008)
		Nearest Neighbor	MP, BP, WS, VP, BCF	Average property value for 3 most similar molecules based on cosine similarity coefficient	Martin et al. (2008); U.S. EPA (2016)
OPERA	2.1	N/A	MP, BP, WS, VP, pKa, HLC, Kow, Koc, BCF, Dow	Weighted k-nearest neighbor using 2D descriptors from PaDEL	Mansouri et al. (2018)

Table 1. Summary of the calculators and calculation methods used in the Physicochemical Properties module.

After selection of the physicochemical properties and calculators, selection of the Calculate data button provides the physicochemical properties output as illustrated in the screen shots below. Selection of the Measured checkbox provides available experimental data from the PHYSPROP database.

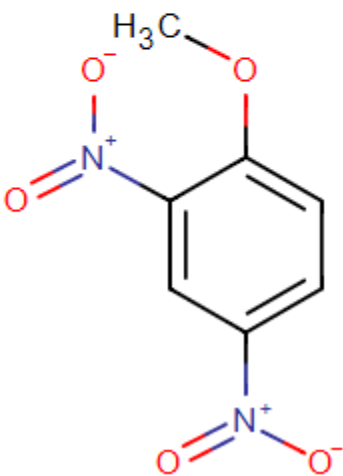
A database of pre-calculated values from the OPERA calculator for several thousand common chemicals has been implemented to improve the speed of retrieval from OPERA. If the given chemical is not in the pre-calculated database, the OPERA calculator will run the models on the fly, causing slower retrieval times for OPERA values.

The geometric mean of the predicted values (not including any measured data or ionization constants) for each selected property from the selected calculators will be automatically calculated and displayed under the Geometric Mean column when predicted values are requested. For some chemicals, the value of the melting point and/or boiling point predicted by one or more of the calculators may be a negative value in units of Celsius. Therefore, to calculate the geometric mean of melting point and boiling point, the calculated values are converted from degrees Celsius to Kelvin before calculating the geometric mean and converting that value back to degrees Celsius.

Calculate Physicochemical Properties Output

Calculate Physicochemical Properties
Tuesday, 2019-July-02 15:55:27 (EST)

- User Inputs



The chemical structure shows a benzene ring with a methoxy group (-OCH₃) at the 1-position, and nitro groups (-NO₂) at the 2 and 4 positions. The nitro groups are shown with a positive charge on the nitrogen atom and a negative charge on one of the oxygen atoms.

Molecular Information	
Entered chemical	1-methoxy-2,4-dinitrobenzene
Initial SMILES	<chem>COC1=CC=C(C=C1[N+](=O)[O-])[N+](=O)[O-]</chem>
Standardized SMILES	<chem>COC1=CC=C(C=C1[N+](=O)[O-])[N+](=O)[O-]</chem>
IUPAC	1-methoxy-2,4-dinitrobenzene
Formula	C ₇ H ₆ N ₂ O ₅
CAS #	119-27-7
Average Mass	198.134
Monoisotopic Mass	198.027671301

- Physicochemical Properties Results

	<input type="checkbox"/> ChemAxon	<input type="checkbox"/> EPI Suite	<input type="checkbox"/> TEST	<input type="checkbox"/> OPERA	<input type="checkbox"/> Geometric Mean	<input type="checkbox"/> Measured
<input type="checkbox"/> All						
Neutral Species Inputs:						
<input type="checkbox"/> Melting Point (°C)		96.56	78.20 HC 87.50 NN 80.30 GC	95.09	87.45	94.50
<input type="checkbox"/> Boiling Point (°C)		319.62	286.50 HC 308.70 NN 315.00 GC	304.17	306.68	208.00
<input type="checkbox"/> Water Solubility (mg/L)	2.68e+2	3.66e+2 WSKOW 2.58e+2 WATERNT	9.54e+1 HC 7.97e+1 NN 5.94e+2 GC	3.21e+2	2.33e+2	1.55e+2
<input type="checkbox"/> Vapor Pressure (mmHg)		1.38e-4	2.06e-4 HC 1.14e-4 NN 2.17e-4 GC	3.05e-4	1.85e-4	N/A
<input type="checkbox"/> Ionization Constant	none			pKa ₁ : 7.25		
<input type="checkbox"/> Henry's Law Constant (atm·m ³ /mol)		4.98e-9		5.52e-7	5.23e-8	N/A
<input type="checkbox"/> Octanol/Water Partition Coefficient (log)	1.74 KLOP 1.70 VG 1.65 PHYS	1.71		1.94	1.75	N/A
<input type="checkbox"/> Organic Carbon Partition Coefficient (log(L/kg))		2.38 MCI 2.37 KOW		2.53	2.42	
<input type="checkbox"/> Bioconcentration Factor (log(L/kg))		0.80 REG 0.68 A-G	0.73 SM 0.10 HC 0.48 NN 0.96 GC	0.98	0.68	
<input type="checkbox"/> Bioaccumulation Factor (log(L/kg))		0.68 A-G			0.68	
pH-Dependent Inputs at pH: <input type="text" value="7.0"/>						
<input type="checkbox"/> Octanol/Water Distribution Coefficient (log)	1.74 KLOP 1.70 VG 1.65 PHYS			1.56	1.66	
<input type="checkbox"/> Water Solubility (mg/L)	-2.87e+3				-2.87e+3	
	Available	Unavailable				

Cancel

Clear data

Calculate data

Generate Transformation Products Workflow

Selection of the Generate Transformation Products Workflow provides the screen shot below illustrating the workflow overview. Click on the “Run single chemical” link to submit a single chemical for processing, or click on the “Run batch file” link to submit a batch file.

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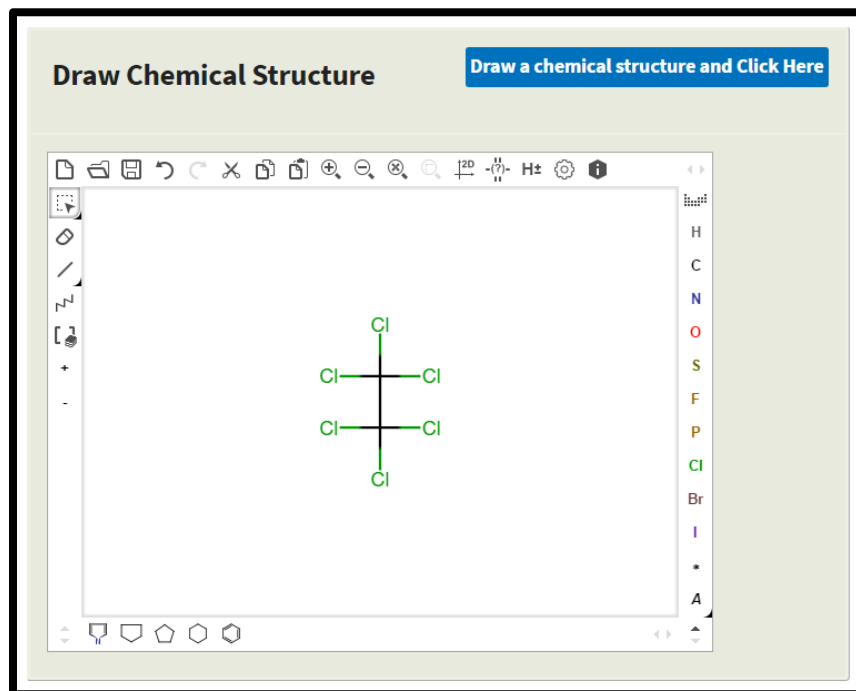
Generate Transformation Products Overview

This workflow allows you to predict transformation products based on the selection and execution of the reaction libraries that encode the process science for transformation processes. You have the option to enter an individual chemical through the Chemical Editor or through batch mode (select Batch tab). Entering the Reaction Pathway Simulator will allow you to select your reaction library of interest based on your selection of reaction conditions.

```
graph TD; A[Define Reaction Conditions] --> B[Select Reaction Libraries]; B --> C[Chemical Editor]; B --> D[Reaction Pathway Simulator]; C --> E[Physicochemical Properties Calculator]; D --> E;
```

The flowchart illustrates the workflow for generating transformation products. It starts with two parallel paths: 'Define Reaction Conditions' and 'Select Reaction Libraries'. Both paths lead to the 'Chemical Editor' and the 'Reaction Pathway Simulator'. The 'Chemical Editor' and 'Reaction Pathway Simulator' both lead to the 'Physicochemical Properties Calculator'.

For this demonstration, hexachloroethane has been entered into the Chemical Editor as illustrated in the screen shot below.



The first required input is the selection of one or more reaction libraries based on the transformation pathways of interest. Three reaction libraries, including abiotic hydrolysis, abiotic reduction and human phase I metabolism, are currently available in CTS. Reaction libraries for photolysis and anaerobic biodegradation are currently under development, and a seamless linkage to a reaction library for aerobic biodegradation will be available in the next version of the CTS. There are available options for the selection of one or multiple reaction libraries (see screen shot below):

- Reaction System Conditions
- OCSPP Harmonized Test Guidelines
- User Selected (Advanced)

The OCSPP Harmonized Test Guidelines specify EPA/OECD-recommended methods to generate data that is submitted to EPA to support:

- The registration of a pesticide under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA);
- The decision-making process supporting potential regulation of an industrial chemical under the Toxic Substances Control Act (TSCA)

Options for selecting Reaction Libraries

Reaction System Guidelines
 OCSPP Guidelines
 User selected (advanced)

Reaction Libraries	
<input type="checkbox"/>	Abiotic Hydrolysis
<input type="checkbox"/>	Aerobic Biodegradation
<input type="checkbox"/>	Photolysis
<input type="checkbox"/>	Abiotic Reduction
<input type="checkbox"/>	Anaerobic Biodegradation
<input type="checkbox"/>	Human Phase 1 Metabolism

Reaction Options	
Max number of generations:	1 ▼

Clear
Back
Submit

Selection of the Reaction System Conditions provides two options for reaction systems: Environmental or Mammalian.

Selection of the Environmental Reaction System provides the option to select respiration type: Aerobic or Anaerobic.

Selection of anaerobic respiration opens the window with the reaction libraries selected for the transformation pathways that are currently available and will potentially occur under these reaction conditions, which includes abiotic hydrolysis and abiotic reduction (see screen shot below).

Options for selecting Reaction Libraries

Reaction System Guidelines
 OCSPP Guidelines
 User selected (advanced)

Reaction system

Environmental
 Mammalian

Select a respiration type

▼

Reaction Libraries

<input checked="" type="checkbox"/>	Abiotic Hydrolysis
<input type="checkbox"/>	Aerobic Biodegradation
<input type="checkbox"/>	Photolysis
<input checked="" type="checkbox"/>	Abiotic Reduction
<input type="checkbox"/>	Anaerobic Biodegradation
<input type="checkbox"/>	Human Phase 1 Metabolism

Reaction Options

Max number of generations:
 ▼

Clear
Back
Submit

Selection of aerobic respiration opens the window with the reactions libraries selected that are currently available and will potentially occur under these conditions, which currently includes only abiotic hydrolysis.

Reaction System Guidelines

Selection of Reaction System Guidelines

Selection of mammalian reaction systems opens the window with the human phase I metabolism reaction library selected as shown in the screen shot below. This is the only option available for the mammalian reaction system.

Options for selecting Reaction Libraries

Reaction System Guidelines
 OCSPP Guidelines
 User selected (advanced)

Reaction system

Environmental
 Mammalian

Reaction Libraries	
<input type="checkbox"/>	Abiotic Hydrolysis
<input type="checkbox"/>	Aerobic Biodegradation
<input type="checkbox"/>	Photolysis
<input type="checkbox"/>	Abiotic Reduction
<input type="checkbox"/>	Anaerobic Biodegradation
<input checked="" type="checkbox"/>	Human Phase 1 Metabolism

Reaction Options	
Max number of generations:	2 ▼

Clear
Back
Submit

The second option for the selection of reaction libraries is through the selection of the Office of Chemical Safety and Pollution Prevention (OCSPP) Fate, Transport, and Transformation (Series 835) or Health Effects (Series 870) Guidelines.

Selection of the Fate, Transformation Series provides three options:

- Laboratory Abiotic Transformation Test Guidelines
- Transformation in Water and Soil Test Guidelines
- Transformation Chemical-Specific Test Guidelines

As an example, selection of the Laboratory Abiotic Transformation Test Guidelines shows that both the abiotic hydrolysis and abiotic reduction are appropriate selections for this option as shown in the screen shot below.

Options for selecting Reaction Libraries

Reaction System Guidelines OCSPP Guidelines User selected (advanced)

OECD Selection

Fate, Transport, and Transformation (Series 835) Health Effects (Series 870)

Fate, Transport, and Transformation

Laboratory Abiotic Transformation Guidelines ▼

Reaction Libraries

<input checked="" type="checkbox"/>	Abiotic Hydrolysis
<input type="checkbox"/>	Aerobic Biodegradation
<input type="checkbox"/>	Photolysis
<input checked="" type="checkbox"/>	Abiotic Reduction
<input type="checkbox"/>	Anaerobic Biodegradation
<input type="checkbox"/>	Human Phase 1 Metabolism

Reaction Options

Max number of generations: ▼

Selection of Health Effects provides one option for selection of a reaction library (i.e., Human Phase I Metabolism) as shown in the screen shot below.

Choose Reaction System Descriptions or OCSPP Test Guidelines to help guide the selection of the appropriate reaction libraries, or choose User Selection to manually select the reaction libraries to use for generating transformation products. Then set the Reaction Options and click submit.

Options for selecting Reaction Libraries

Reaction System Guidelines OCSPP Guidelines User selected (advanced)

OECD Selection

Fate, Transport, and Transformation (Series 835) Health Effects (Series 870)

Reaction Libraries

<input type="checkbox"/>	Abiotic Hydrolysis
<input type="checkbox"/>	Aerobic Biodegradation
<input type="checkbox"/>	Photolysis
<input type="checkbox"/>	Abiotic Reduction
<input type="checkbox"/>	Anaerobic Biodegradation
<input checked="" type="checkbox"/>	Human Phase 1 Metabolism

Reaction Options

Max number of generations:

The third option for the selection of reaction libraries is through the selection of the “User selected” button as shown in the screen shot below. This option provides the ability to select amongst the currently available reaction libraries. After selecting reaction libraries through one of the three options, the option to change the Reaction Options is given:

- **Max number of generations:** the maximum number of generations of transformation products that will be generated. The default value is set at one, and the maximum value is four.

Options for selecting Reaction Libraries

Reaction System Guidelines OCSP Guidelines User selected (advanced)

Reaction Libraries	
<input type="checkbox"/>	Abiotic Hydrolysis
<input type="checkbox"/>	Aerobic Biodegradation
<input type="checkbox"/>	Photolysis
<input checked="" type="checkbox"/>	Abiotic Reduction
<input type="checkbox"/>	Anaerobic Biodegradation
<input type="checkbox"/>	Human Phase 1 Metabolism

Reaction Options

Max number of generations:

[Clear](#) [Back](#) [Submit](#)

After selection of the reaction libraries and reaction options have been made, click the Submit button to generate transformation products. The screen shot below summarizes the input data and provides the first generation of transformation products (the default value) based on execution of the abiotic hydrolysis and reduction libraries as previously selected.

Generate Transformation Products Output

Generate Transformation Products

Wednesday, 2018-June-06 09:06:39 (EST)

- User Inputs

Molecular Information	
Entered chemical	hexachloroethane
Standardized SMILES	<chem>ClC(Cl)(Cl)C(Cl)(Cl)Cl</chem>
Initial SMILES	<chem>ClC(Cl)(Cl)C(Cl)(Cl)Cl</chem>
IUPAC	hexachloroethane
Formula	C2Cl6
CAS #	67-72-1
Average Mass	236.72 g/mol
Monoisotopic Mass	233.8131162 g/mol

Reaction Pathway Simulator	
Libraries	abiotic_reduction
Generation Limit	2

- Select (right click) a product in the tree below to view its molecular information.
- Left click a product in the tree below to view its transformation product and formation pathway.
- Pan reaction pathways tree by holding down the left click button anywhere in the blue area and moving the mouse.
- Zoom in and out with the mouse wheel.

Display up to:

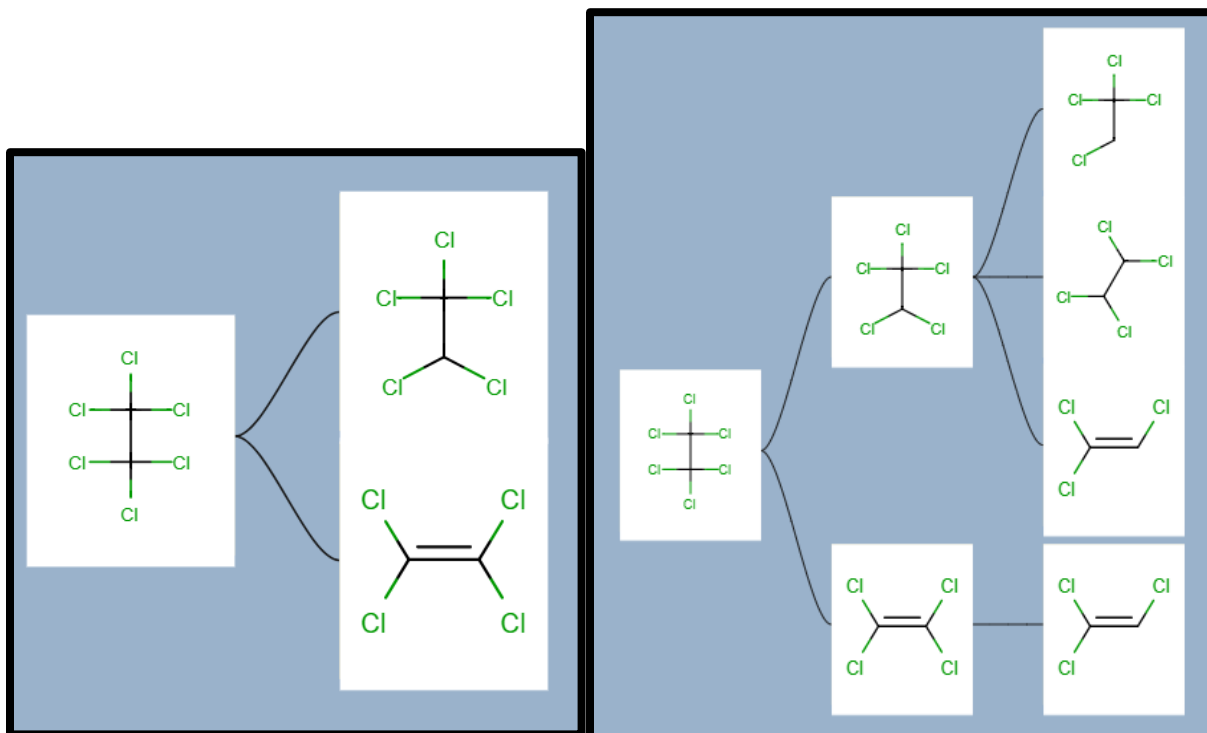
2nd gen ▼

Total Products:6

+ View Molecular Information

+ Calculate Physicochemical Properties

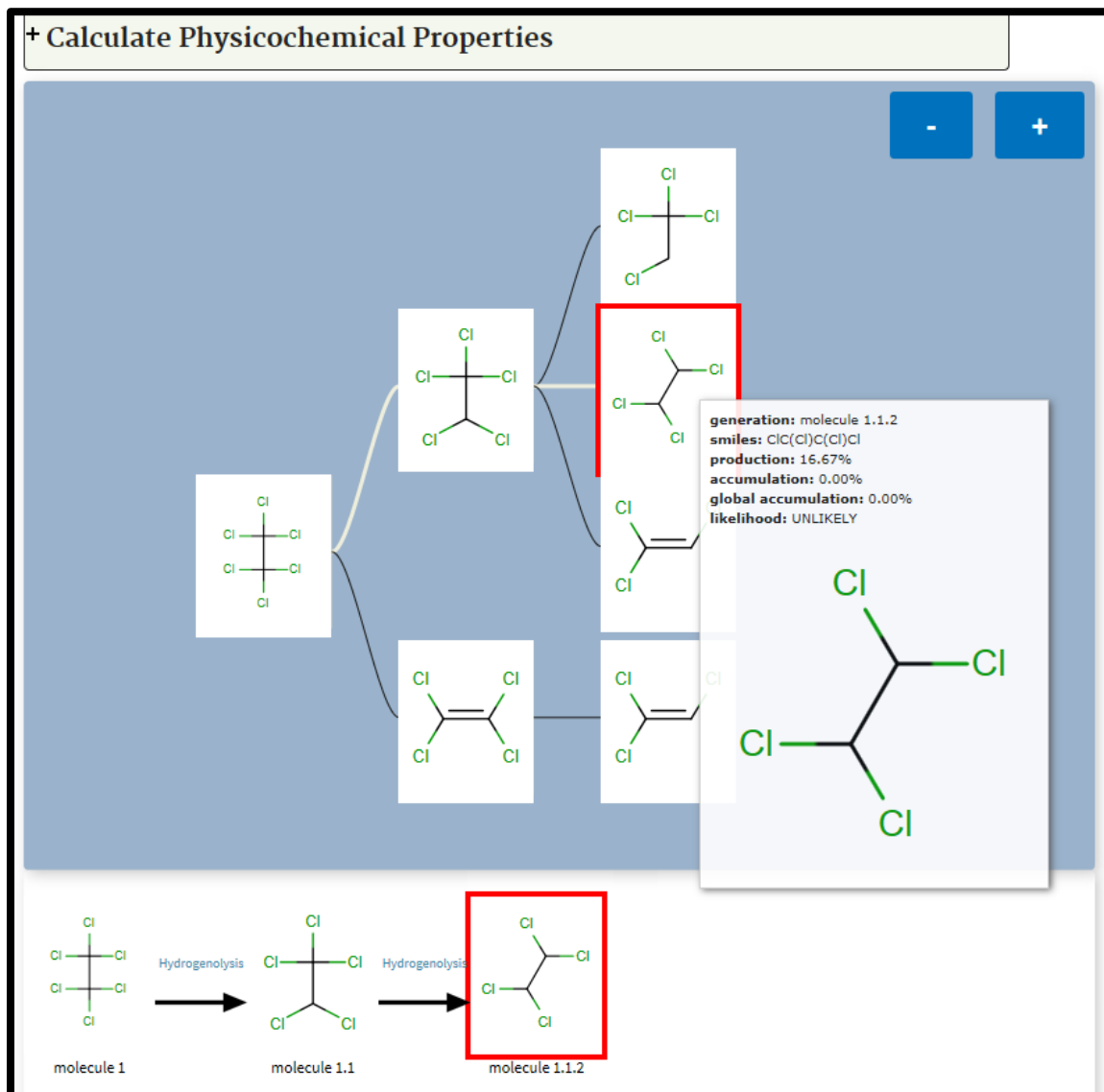
The number of viewed generations can be increased by changing the number of generations in the “Display up to” window shown in the screen shot above. The screen shot below on the left illustrates the reaction pathway map for the formation of one generation of products. The screen shot below on the right illustrates the reaction pathway map for the formation of two generation of products. Note, that the number of observed generations cannot exceed the Generation Limit set on the previous screen. The screen shot above indicates the total number of products that are predicted. If the total product = 0, then the user is to assume the selected reaction process does not occur for the parent chemical of interest.



By placing the cursor over a product, a popup box appears, with a molecule number that signifies its place in the reaction pathway map. For this example, tetrachloroethane (1.1.2) is the 2nd product formed in the second generation from the 1st product (i.e., pentachloroethane, 1.1), which was formed in the first generation from hexachloroethane as shown in the screen shot below. Below the molecule number are values for production, accumulation, global accumulation, and likelihood. The production, accumulation, and global accumulation values are explained in detail in a separate document. Metabolites considered “likely” (having a global accumulation of at least 10%) will be highlighted with a blue border in the tree.

By left-clicking on a product in the reaction pathway map, the next generation of transformation products that are predicted to form from a selected product, as well as the reactions that form them, are displayed under the reaction pathway map, as shown in the screen shot below. For each step in the transformation sequence, the name of the reaction scheme that generated the product is provided above the arrow between the parent and product. Clicking on a transformation

scheme name opens a new browser tab with detailed information about the scheme from the Reaction Library documentation. By right-clicking on a product, the molecular and metabolite information for the product is displayed above the reaction pathway map. The selected metabolite will be highlighted with a red border in the tree, as shown in the screenshot below. The “Get transformation products” button immediately below the molecular information box can be clicked to open a new browser tab with the product entered as the chemical of interest in the Generate Transformation Products workflow.



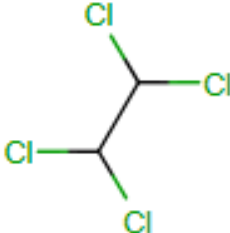
Below the Molecular Information table, clicking on the Calculate Physicochemical Properties dropdown box provides the various options for physicochemical properties and calculators to be applied to the selected transformation product, as shown in the screen shots below.

The selected physicochemical properties will be calculated and displayed in the results table. For example, selection of the All and ChemAxon, EPI Suite, TEST and OPERA buttons and Clicking on the Calculate Physicochemical Properties link provides the screen on the results for the selected physicochemical calculators for the selected metabolite, tetrachloroethane, as shown in the screen shot below.

Display up to:
2nd gen ▼

Total Products:6

- View Molecular Information



The image shows the skeletal structure of 1,1,2,2-tetrachloroethane, a two-carbon chain with two chlorine atoms on each carbon.

Molecular Information	
smiles	<chem>ClC(Cl)C(Cl)Cl</chem>
routes	Hydrogenolysis
generation	molecule 1.1.2
formula	C2H2Cl4
lupac	1,1,2,2-tetrachloroethane
mass	167.84
exactMass	165.8910609

Calculate Physicochemical Properties

Calculate physicochemical properties for: selected metabolite

Select physicochemical properties to gather for selected metabolite, then click "Calculate data" below..

	<input checked="" type="checkbox"/> ChemAxon	<input checked="" type="checkbox"/> EPI Suite	<input checked="" type="checkbox"/> TEST	<input checked="" type="checkbox"/> OPERA	Geometric Mean	<input checked="" type="checkbox"/> Measured
<input checked="" type="checkbox"/> All						
Neutral Species Inputs:						
<input checked="" type="checkbox"/> Melting Point (°C)		-48.66	-48.80 HC -44.60 NN -27.90 GC	-39.83	-42.65	-43.80
<input checked="" type="checkbox"/> Boiling Point (°C)		149.90	140.60 HC 130.80 NN 140.50 GC	147.58	140.39	146.50
<input checked="" type="checkbox"/> Water Solubility (mg/L)	4.29e+2	1.25e+3 WSKOW 1.85e+3 WATERNT	2.73e+3 HC 3.28e+3 NN 7.42e+2 GC	2.96e+3	1.37e+3	2.83e+3
<input checked="" type="checkbox"/> Vapor Pressure (mmHg)		4.72e+0	5.06e+0 HC 6.91e+0 NN 5.13e+0 GC	7.29e+0	5.40e+0	1.33e+1
<input checked="" type="checkbox"/> Ionization Constant	none			none		
<input checked="" type="checkbox"/> Henry's Law Constant (atm·m ³ /mol)		1.51e-3		5.01e-4	1.51e-3	3.66e-4
<input checked="" type="checkbox"/> Octanol/Water Partition Coefficient (log)	3.54 KLOP 2.06 VG 2.91 PHYS	2.19		2.35	2.68	2.39
<input checked="" type="checkbox"/> Organic Carbon Partition Coefficient (log(L/kg))		1.98 MCI 2.07 KOW		1.89	2.03	
<input checked="" type="checkbox"/> Bioconcentration Factor (log (L/kg))		1.24 REG 1.29 A-G	1.36 SM 1.04 HC 1.09 NN 1.27 GC	1.07	1.22	
<input checked="" type="checkbox"/> Bioaccumulation Factor (log (L/kg))		1.29 A-G			1.29	
pH-Dependent Inputs at						
pH: <input type="text" value="7.0"/>						
<input checked="" type="checkbox"/> Octanol/Water Distribution Coefficient (log)	3.54 KLOP 2.06 VG 2.91 PHYS			2.35	2.84	
<input checked="" type="checkbox"/> Water Solubility (mg/L)	-2.59e+3				-2.59e+3	
	Available	Unavailable				

The screen shot above indicates the total number of products that are predicted. If the total product = 0, then the user is to assume the selected reaction processes do not occur for the parent chemical of interest.

To get physicochemical data for multiple metabolites, select the option for calculating physicochemical properties for up to the first, second, or third generation of metabolites, or for all calculated metabolites from the drop-down menu. Then, select the properties and calculators to be used and click the Calculate data button. The results for multiple metabolites will not be presented in the table as they are for a single metabolite. To view the results for multiple metabolites, download and view the report (as a PDF, CSV, or HTML file) as described below.

Generation of PDF, HTML and CSV Reports

The .pdf, .html and .csv buttons appear on the top right corner of the results page, regardless of the workflow. Clicking on the .pdf button generates a PDF file that can be viewed in the web browser or using free PDF software. The HTML file can be viewed using a web browser.

The PDF and HTML reports are multi-page reports showing the calculated physicochemical data for the parent compound and the selected transformation products. Examples of the PDF and HTML reports are shown below in the first two screen shots.

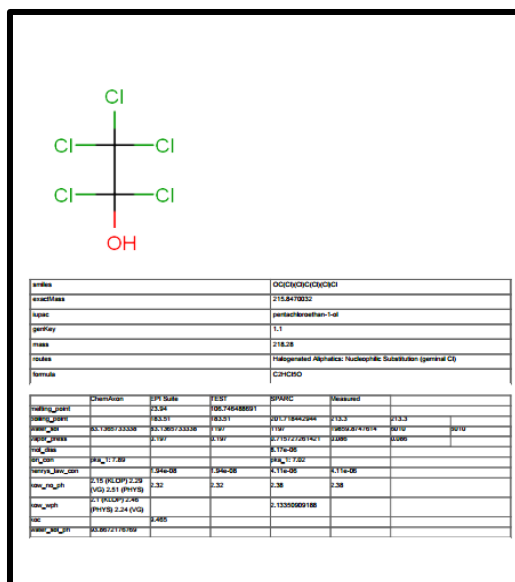
The screenshot displays a report for the compound 1,1,1,2,2,2-hexachloroethane. The report is structured as follows:

- Header:** 1,1,1,2,2,2-hexachloroethane
- Molecular Information:**

Property	Value
SMILES	ClC(Cl)(Cl)C(Cl)(Cl)Cl
MW	332.17
Formula	C2Cl6
Charge	0
Parent Name	1,1,1,2,2,2-hexachloroethane
Parent SMILES	ClC(Cl)(Cl)C(Cl)(Cl)Cl
Parent MW	332.17
Parent Formula	C2Cl6
Parent Charge	0
- Chemical Structure:** A skeletal structure of 1,1,1,2,2,2-hexachloroethane, showing a central carbon-carbon bond with six chlorine atoms attached to the carbons.
- Physicochemical Properties:**

Property	Value
SMILES	ClC(Cl)(Cl)C(Cl)(Cl)Cl
MW	332.17
Formula	C2Cl6
Charge	0
Parent Name	1,1,1,2,2,2-hexachloroethane
Parent SMILES	ClC(Cl)(Cl)C(Cl)(Cl)Cl
Parent MW	332.17
Parent Formula	C2Cl6
Parent Charge	0

PDF Report



HTML Report

The CSV report is generated in a tabular format as shown below in the screen shot.

	A	B	C	D	E	F	G
1	genKey	routes	smiles	iupac	formula	mass	exactMass
2		1	ClC(Cl)(Cl)C(Cl)C(Cl)C(Cl)C(Cl)	hexachlorocyclohexane	C6Cl6	236.72	233.8131
3		1.1 Halogenated Aliphatics: Hydroxylic Substitution: general Cl	OC(Cl)(Cl)C(Cl)C(Cl)C(Cl)C(Cl)	pentachlorocyclohexan-1-ol	C2HCl5O	218.28	215.847
4		1.2 Hydrogenated Aliphatics: Halogenated: general Cl	ClC(Cl)C(Cl)C(Cl)C(Cl)C(Cl)	1,1,1,2,2,2-hexachlorocyclohexane	C2HCl5	202.28	199.8521
5	1.2.1	Hydrogenated Aliphatics: Halogenated: general Cl	ClC=C(Cl)C(Cl)C(Cl)C(Cl)	1,1,2-trichloro-2-(chloromethyl)cyclohexane	C2HCl3	131.38	129.9144
6	1.2.2	Hydrogenated Aliphatics: Halogenated: general Cl	ClC(Cl)=C(Cl)C(Cl)C(Cl)C(Cl)	tetrachlorocyclohexane	C2Cl4	165.82	163.8754
7	1.2.3	Hydrogenated Aliphatics: Halogenated: general Cl	OC(Cl)(Cl)C(Cl)C(Cl)C(Cl)C(Cl)	1,1,2,2-tetrachloro-2-(chloromethyl)cyclohexane	C2H2Cl4O	183.84	181.886
8	1.2.4	Hydrogenated Aliphatics: Halogenated: general Cl	OC(Cl)C(Cl)C(Cl)C(Cl)C(Cl)C(Cl)	1,2,2,2-tetrachloro-1-(chloromethyl)cyclohexane	C2H2Cl4O	183.84	181.886
9	1.2.5	Hydrogenated Aliphatics: Halogenated: general Cl	ClCC(Cl)C(Cl)C(Cl)C(Cl)C(Cl)	1,1,1,2-tetrachloro-2-(chloromethyl)cyclohexane	C2H2Cl4	167.84	165.8911
10	1.2.6	Hydrogenated Aliphatics: Halogenated: general Cl	ClC(Cl)C(Cl)C(Cl)C(Cl)C(Cl)	1,1,2-tetrachloro-2-(chloromethyl)cyclohexane	C2H2Cl4	167.84	165.8911
11		1.3 Vicinal Dichlorides: general Cl	ClC(Cl)=C(Cl)C(Cl)C(Cl)C(Cl)	tetrachlorocyclohexane	C2Cl4	165.82	163.8754
12	1.3.1	Vicinal Dichlorides: general Cl	ClC=C(Cl)C(Cl)C(Cl)C(Cl)	1,1,2-trichloro-2-(chloromethyl)cyclohexane	C2HCl3	131.38	129.9144

CSV Report

References

- Contrera, J.F., Matthews, E.J., Benz, R.D. 2003. Predicting the carcinogenic potential of pharmaceuticals in rodents using molecular structural similarity and E-state indices. *Reg. Toxicol. Pharmacol.* 38: 243–259.
- Hou, T.J., Xia, K., Zhang, W., Xu, X.J. 2004. ADME evaluation in drug discovery. 4. prediction of aqueous solubility based on atom contribution approach, *J. Chem. Inf. Comput. Sci.* 44: 266-275.
- Klopman, G., Li, J.-Y., Wang, S., Dimayuga., M. 1994. Computer automated log P calculations based on an extended group contribution approach. *J. Chem. Inf. Comput. Sci.* 34: 752-781.
- Mansouri, K., Grulke, C.M., Judson, R.S., Williams, A.J. 2016. OPERA models for predicting physicochemical properties and environmental fate endpoints. *J. Cheminform.* 10:10.
- Martin, T.M., Harten, P., Venkatapathy, R., Das, S. Young, D.M. 2008. A hierarchical clustering methodology for the estimation of toxicity, toxicology mechanisms and methods. *Toxicol. Mech. Methods* 18: 251–266.
- Martin, T.M., Young. D.M. 2001. Prediction of the acute toxicity (96-h LC50) of organic compounds in the fathead minnow (*Pimephales Promelas*) using a group contribution method. *Chem. Res. Toxicol.* 14: 1378–1385.
- Meylan, W., P.H. Howard and R.S. Boethling. 1992. Molecular topology/fragment contribution method for predicting soil sorption coefficients. *Environ. Sci. Technol.* 26: 1560-1567.
- Meylan W.M., Howard, P.H. 1995. Atom/Fragment contribution method for estimating octanol-water partition coefficients, *Journal of Pharmaceutical Sciences*, 84: 83-92.
- Meylan, W.M., Howard, P.H., Boethling, R.S. 1996. Improved method for estimating water solubility from octanol/water partition coefficient. *Environ. Toxicol. Chem.* 15: 100-106.
- Szegezdi, J., Csizmadia, F. 2004. [Prediction of dissociation constant using microconstants](#). 27th ACS National Meeting, Anaheim, California, March 28-April 1, 2004. Szegezdi, J., Csizmadia, F. 2007. [A method for calculating the pKa values of small and large molecules](#). American Chemical Society Spring meeting, March 25-29th, 2007.
- US EPA. 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11. United States Environmental Protection Agency, Washington, DC, USA.
- U.S. EPA 2016. User's Guide for T.E.S.T. (version 4.2) (Toxicity Estimation Software Tool): A Program to Estimate Toxicity from Molecular Structure, EPA/600/R-16/058. United States Environmental Protection Agency, Washington, DC, USA.
- Viswanadhan, V.N., Ghose, A.K., Revankar, G.R., Robins, R.K. 1989. Atomic physicochemical parameters for three-dimensional structure directed quantitative structure-activity relationships. 4. Additional parameters for hydrophobic and dispersive interactions and their application for an automated superposition of certain naturally occurring nucleoside antibiotics. *J. Chem. Inf. Comput. Sci.* 29: 163-172.