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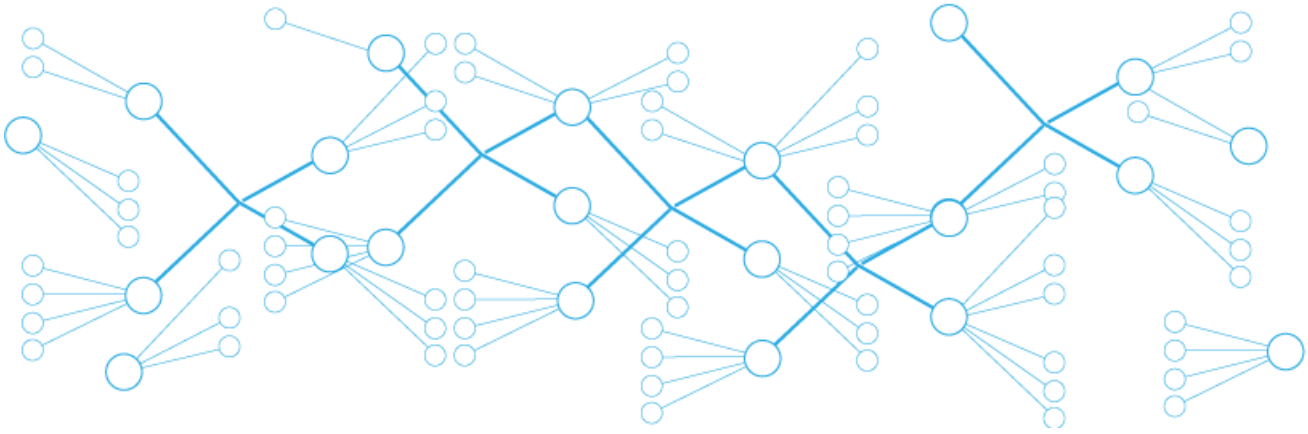
International QSAR Foundation

Effectopedia

The Online Encyclopedia of Adverse Effect Pathways

About Effectopedia

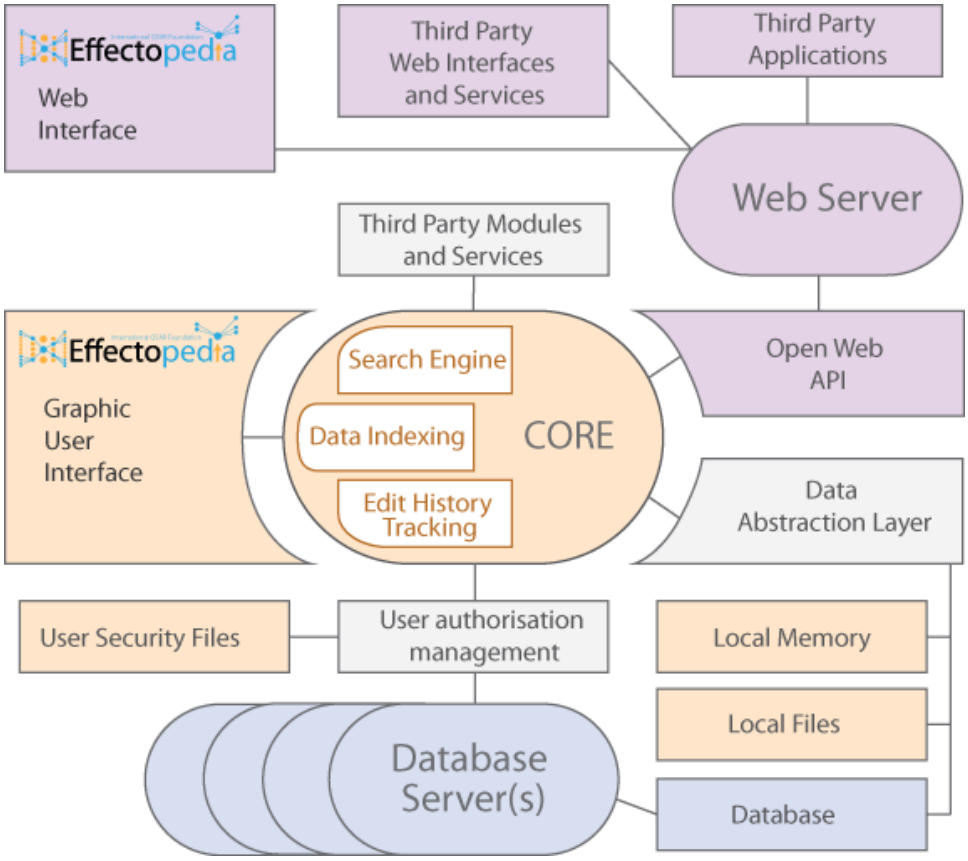
Effectopedia is an open knowledge aggregation and collaboration tool that provides a means of describing Adverse Outcome Pathways (AOPs) in an encyclopedic manner. It was conceived at the International QSAR Foundation in 2006 to overcome a major technological barrier in QSAR models for predicting in vivo risks. AOPs can be used to forecast and explain observable adverse effects of chemicals under a wide variety of experimental conditions and animal test guidelines.
The basic structure of toxicological evidence in Effectopedia consists of documented "cause-link-effect" relationships which are linked to form toxicity pathways between molecular events and safety assessment endpoints as AOPs. Special Effectopedia tools will simplify the creation of complex biological response networks as well as for scaling experimental dosimetry across different levels of biological organization. The Wiki architecture, while enabling many disciplines to contribute discrete mechanistic information at strategic points along the AOP, will also catalyze greater scientific discussion by specialists who may not normally collaborate or read each other's literature.



Effectopedia Architecture

Effectopedia is designed to accommodate broad range of possible usage scenarios, separating the user interface from data and core functionalities. This allows Effectopedia platform to be used as standard

standalone application operating on local files and/or remote database servers. It also can provide access to the same data sources when used as a server side application with web interface, or as service providing open web Application Programming Interface (API) to third party applications (like OECD Toolbox)



Effectopedia global architecture.

Effectopedia has modular architecture which allows different usage patterns. Gray shaded boxes represent modules that can be executed on local machine as part of standalone application. Orange shaded modules provide the core Effectopedia functionality. They have mixed usage: as server side and / or as application embedded modules. Blue shaded modules provide access to database (local or remote) functionality. Purple shaded modules provide web interface to the Effectopedia core functionalities. Modules shown in bold outline are currently implemented.

This flexibility is achieved by highly modular architecture shown on the fugure above. Each module encapsulates given functionality implementing universal access methods for communication with other modules. In turn modules consist of packages and packages of classes which further break the complex functionalities to simple straightforward tasks.

The two primary configurations of modules that are going to be utilized by International QSAR Foundations could be conventionally called: Effectopedia Application and Effectopedia Web Interface targeted at contributors and general users (readers) respectively.

Effectopedia application includes graphic user interface, core module, user authorization management and security files, data abstraction layer, local memory and files modules, and database module required for access to the centralized IQF maintained database of pathways referred simply as centralized Effectopedia database. The primary purpose of Effectopedia application (executed as local program, web start application or applet) is to serve as the main visual editor of pathways providing user friendly tool for collaborative creation/ exploration / utilization of pathways.

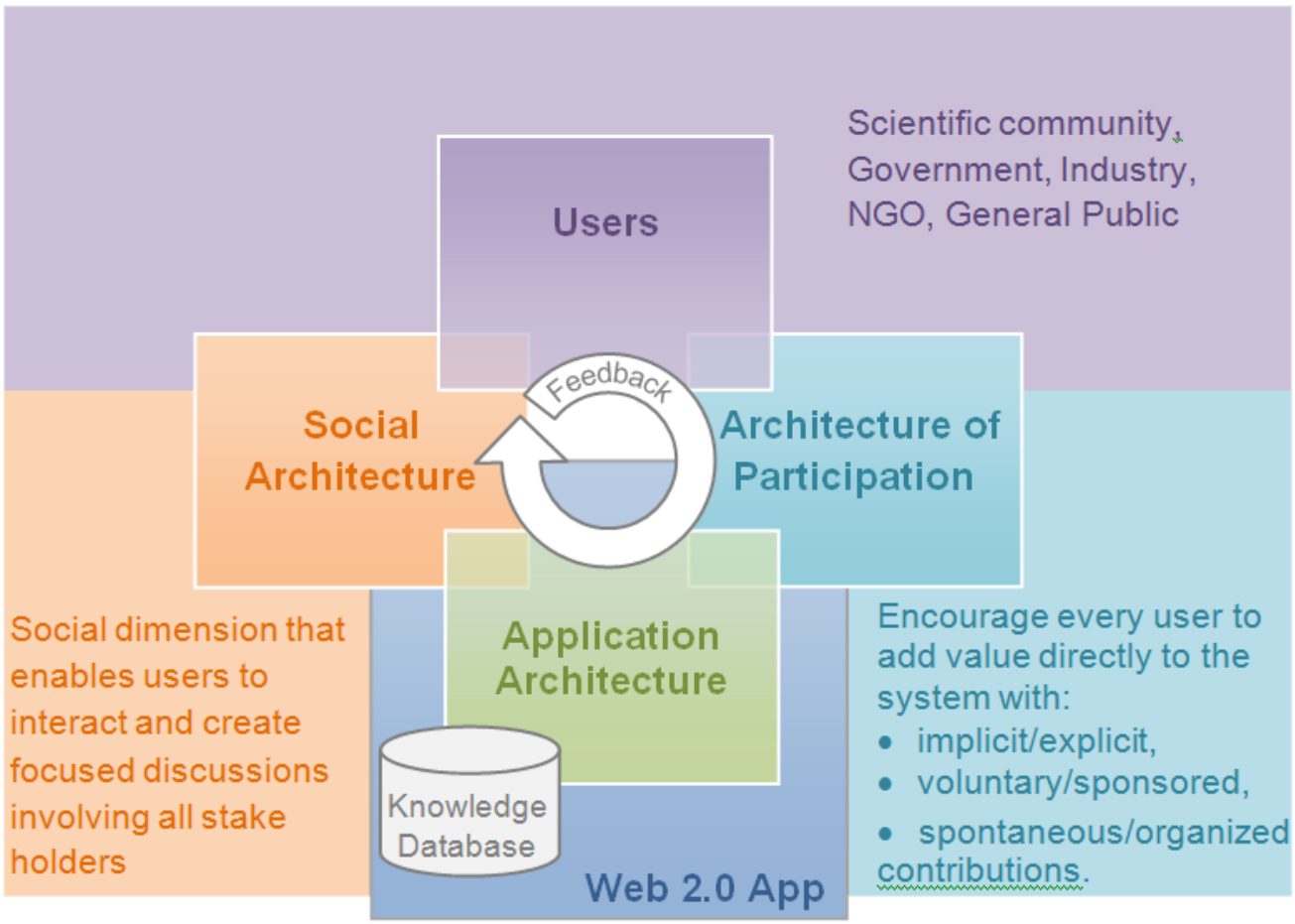
The Effectopedia Web Interface provides Wiki-like search engine optimized articles of the adverse outcome pathways (AOP) in a relational manner. For each AOP, there is a major overview wiki article linked to in-depth descriptions of the biological response sequences that link a chemical-induced molecular effect to the adverse outcomes needed for safety assessment.

Centralized Effectopedia Database

The Centralized Effectopedia Database is the main public data repository maintained by International QSAR Foundation, which stores all user contributed knowledge along with the full edit history. The Effectopedia database utilizes version control system similar to Apache subversion, which employs the copy-modify-merge model as an alternative to locking. In this model, each user's client contacts the centralized repository and creates a personal working copy. Users then work simultaneously and independently, modifying their private copies. Finally, the private copies are merged together into a new, final version. Effectopedia automatically merges the unrelated edits and provides users with a tool assisting contributors to merge the conflicting edits.

Technology of Participation

Effectopedia is designed in the spirit of web 2.0 application concepts where wide range of users are encouraged to interact and contribute to the system in variety of ways



Adapted from Dion Hinchcliffe (Transforming Software Architecture for the 21st Century (September 2009)).

Using Help

The Effectopedia help system is divided in several major sections in order to cover the conceptual and practical aspects of the Effectopedia application. Conceptual aspects are covered in the Concept and About sections of the help introducing the main terms and design principles respectively. The practical information on how to use Effectopedia interface for various tasks is provided in the user interface section of the help. The information in this section provides more general overview of the available features while the context sensitive help system gives more targeted concise help depending on the current context. Additionally some of the major usage scenarios are covered in the getting started section of the help.

Using Context Sensitive Help System

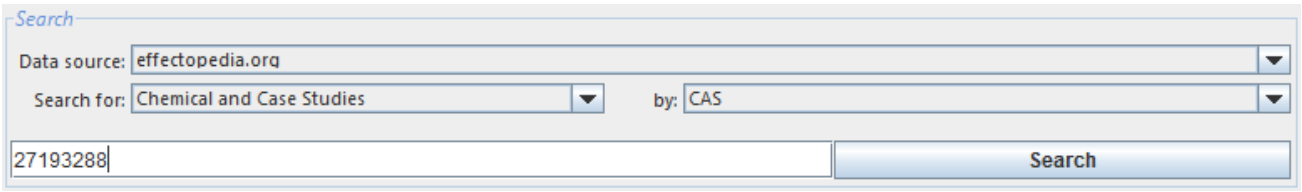
The Effectopedia context sensitive help system provides help for the interface component under the cursor taking into consideration current interface settings, tasks and modes. For example context sensitive help in the search interface provides the following two versions of the context help for the same component of the interface (the query text field):

> **Search for a Chemicals and Case Studies**
> Using only digits type the CAS registry number of the chemical you are looking for and press search. The search query will return all matching AOPs, effects and case studies.

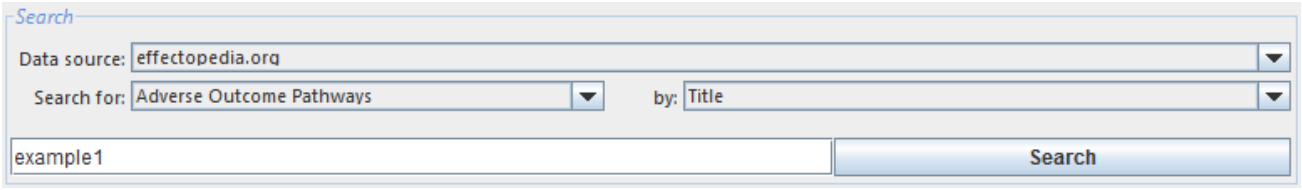
and

> **Search for a Molecular Initiating Events, Adverse Biological Effects or Hazard Assessment Endpoints**
> Type words from the effect title and press search. Please note that currently only case insensitive match of whole words is supported. After the search is complete, all matching Molecular Initiating Events, Adverse Biological Effects, and Hazard Assessment Endpoints will be listed.

depending on whether the interface is currently setup for searching chemicals or case studies by CAS number or



Adverse outcome pathways by title

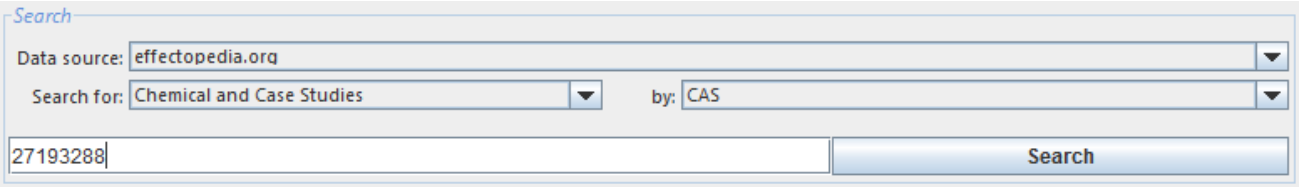


Most of the user interface components are nested in titled or labeled sections and in general the deeper the nesting is the more specific the context sensitive help becomes.

Building a search query to find a chemical or case study

In order to find chemical substance or case study that includes particular chemical you can use the following steps:

1. Go to welcome page and select "Review mechanistic information for individual chemicals"
2. Select the data source where the chemical or case studies are going to be searched in. By default the centralized Effectopedia database will be queried. In case you have a custom servers specified, or local files loaded you can choose to search in them or alternatively select the option All which will allow you to execute the search across all data sources.
3. If you followed the link from step 1. the interface is will be setup to look for Chemical and Case Studies by CAS registry number.
4. If you would like to make the search by IUPAC Name, Smiles or Mol. Formula please select the appropriate option in the by: drop down box
5. Enter search term(s) - CAS registry number, IUPAC Name, Smiles or Mol. Formula depending on your choice in step 4.
6. Execute search by clicking on Search button.



Alternatively you can find any case study by searching for its downstream elements like MIE, adverse biological effects and outcomes. :

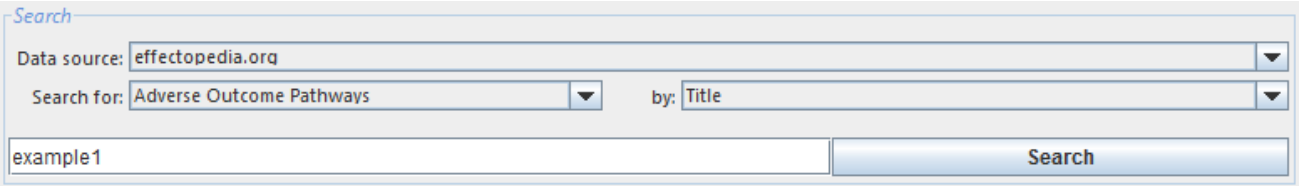
1. Go to welcome page and select "Review the current status of existing adverse outcome pathways"
2. Select the data source where you want to search the pathway. By default the centralized Effectopedia database will be queried. In case you have a custom servers specified, or local files loaded you can choose to search in them or alternatively select the option All which will allow you to execute the search across all data sources.
3. Select any of the following options Molecular Initiating Events, Adverse Biological Effects (including Adverse Outcomes), Hazard Assessment Endpoints.

4. Select the field by which you want to perform the search. Available options are Title, Keywords, Groups and Context.
5. If you have selected context you need to additionally specify the context dimension which you are going to use for the search.
6. Enter search term with respect to selected search fields in steps 4. and 5.
7. Execute search by clicking on Search button.

Building a search query to find AOPs or Effects

Search interface form is designed to be completed from top to bottom and from left to right. By doing so you will be able to specify what are you looking for and which fields have to be used to match against the search terms you are entering. Use the following steps in order to find a specific adverse outcome pathway:

1. Go to welcome page and select "Review the current status of existing adverse outcome pathways"
2. Select the data source where you want to search the pathway. By default the centralized Effectopedia database will be queried. In case you have a custom servers specified, or local files loaded you can choose to search in them or alternatively select the option All which will allow you to execute the search across all data sources.
3. If you followed the link from step 1. the interface is will be setup to look for Adverse Outcome Pathway by title.
4. If you would like to make the search by keyword please select Keywords in the by: drop down box
5. Enter search terms - fragment or title or keywords depending on your choice in step 4.
6. Execute search by clicking on Search button.



Alternatively you can find any pathway by searching for one its elements like MIE, adverse biological effects and outcomes. :

1., 2. Follow the first two steps from above
3. Select any of the following options Molecular Initiating Events, Adverse Biological Effects (including Adverse Outcomes), Hazard Assessment Endpoints.
4. Select the field by which you want to perform the search. Available options are Title, Keywords, Groups and Context.
5. If you have selected context you need to additionally specify the context dimension which you are going to use for the search.

6. Enter search term with respect to selected search fields in steps 4. and 5.
7. Execute search by clicking on Search button.

Introduction

The process of building an adverse outcome pathway or a case study follows the same logical steps. The main technical difference between them is that the case studies usually start with single chemical or structural alert and can include more than one Adverse Outcomes while AOPs can include multiple chemicals or structural alerts that lead to a single Adverse Outcome. Use the following steps to build an AOPs or Case Study:

1. Chose Effectopedia space dimensions.
2. Build pathway/case study structure.
3. Add qualitative information.
4. Add quantitative information.
5. Publish your contribution.

1. Chose Effectopedia Space Dimensions

Effectopedia offers multidimensional context pathway space in which elements of the pathways are defined. In the pathway space viewer a two dimensional projection of that space is shown. The selection of the most appropriate projection can be based on different criteria like:
- the availability of the information for the locations of pathway elements.
- or visualization of important branching of the pathway across the chosen dimensions.
Horizontal axis is set by default to Level of biological organization since it does lead to clear delineation of molecular to higher level of organization effects and also provides a natural place for chemical substances and structural alerts in the beginning of the pathways or case studies. Vertical axis is currently set to gender by default but this setting might be subject to change if the majority of the pathways entered in Effectopedia are better perceived in different projection. Both axis can be changed by right clicking on the axis label and selection of a new axis from the pop menu.

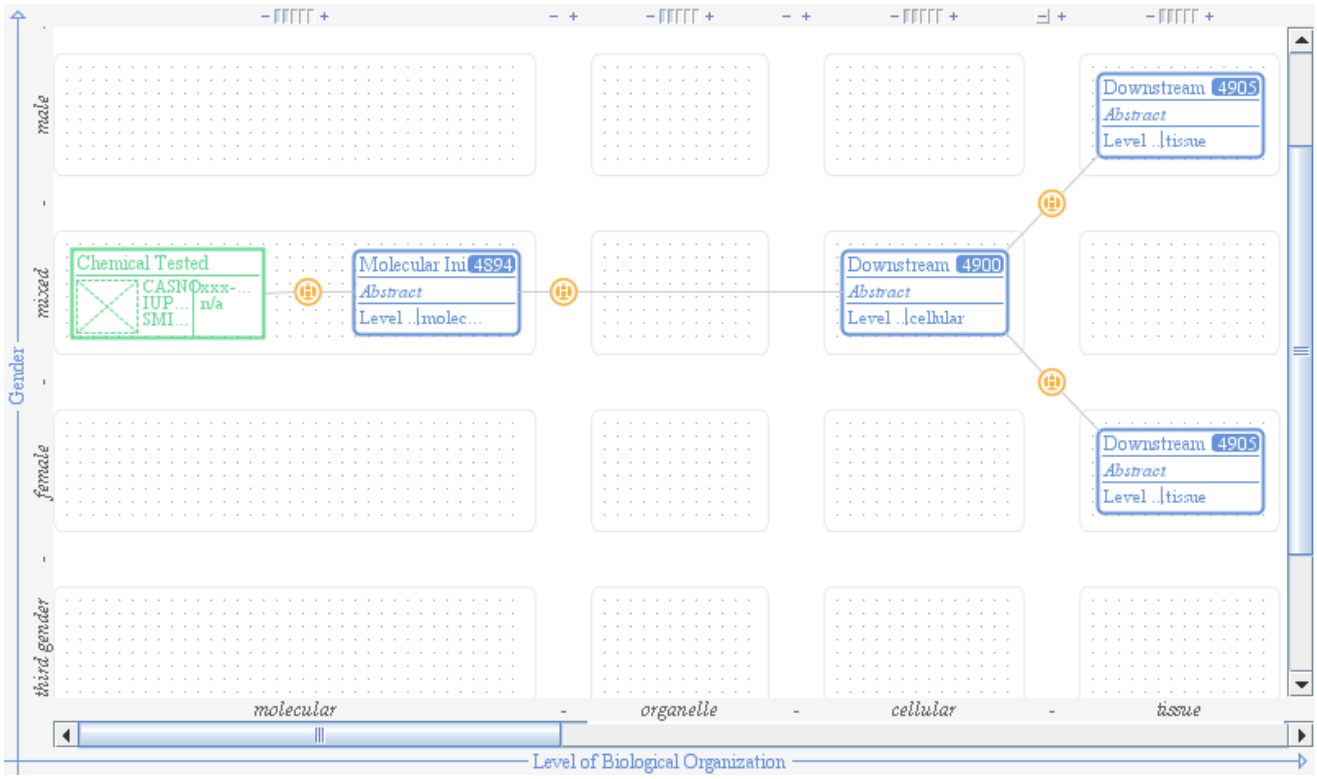
Go to next step: Build pathway/case study structure or back to introduction.

2. Build pathway structure

Before contributing any new information to Effectopedia please make extensive search to find out if the information you are trying to enter is not already available.

Effectopedia offers variety of tools and wizards for quick visual construction of the pathway structure. The technical details how to use and apply this tools can be found in pathway viewer modes section of the help. In this section the use of the CLET tool (most suitable for building branches in pathways will be illustrated. As an example of the usage of the CLET tool the first steps needed for

recreation of the Estrogen Binding pathway structure originating at the chemical Octylphenol (shown on the figure below) will be provided.



1. If needed change vertical axis to Gender and horizontal axis to Level of Biological Organization.
2. Select CLET tool
3. Move the cursor over the segment with coordinates (molecular, mixed)
4. Click in the middle of the segment while the whole segment is highlighted in blue. This will create an active Structural Alert generic object.
5. While over the object (segment is still all highlighted) click once to change the Structural alert to simple Chemical Substance
6. Move the cursor to the right and while in the East corner of the (molecular, mixed) segment click once to create new link
7. Move the cursor to the right of the link, but keep it in the boundaries of the (molecular, mixed) segment. Keep moving to the right until the East area of the link is highlighted. Click once to create a new MIE and connect it with the link from the previous step.
8. Move the cursor in the white space to the right of the (molecular, mixed) segment. Click once to place a new link. This link signifies a transition across the Level of Biological Organization axis.
9. Move the cursor to the right until you reach the segment with coordinates (cellular, mixed), click once while the whole segment is highlighted to create the first downstream effect.

10. Move the cursor with to the white space with coordinates between mixed and male and between cellular and tissue. Click there to create a link signifying that in the transition in both axis to tissue level effect for male.

11. Move the cursor to the segment with the segment with coordinates (tissue, male) and click once while the whole segment is highlighted to create the next downstream effect.

12. Move the cursor over the first Downstream effect in the (cellular, mixed) segment until the whole segment is highlighted. Click once to activate the pathway element. With this action you choose this downstream effect as a origin of the next link.

13.Move the cursor with to the white space with coordinates between mixed and female and between cellular and tissue. Click there to create a link signifying that in the transition in both axis to tissue level effect for female.

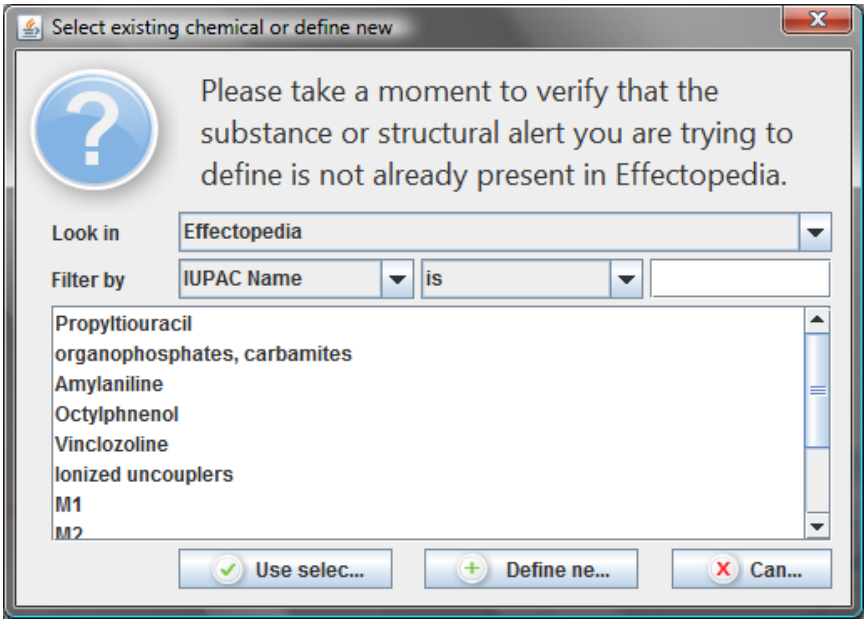
14. Move the cursor to the segment with the segment with coordinates (tissue, female) and click once while the whole segment is highlighted to create the next downstream effect.

With this your sample pathway segment has been recreated.

Go to next step: Add qualitative information or back to Chose Effectopedia space dimensions.

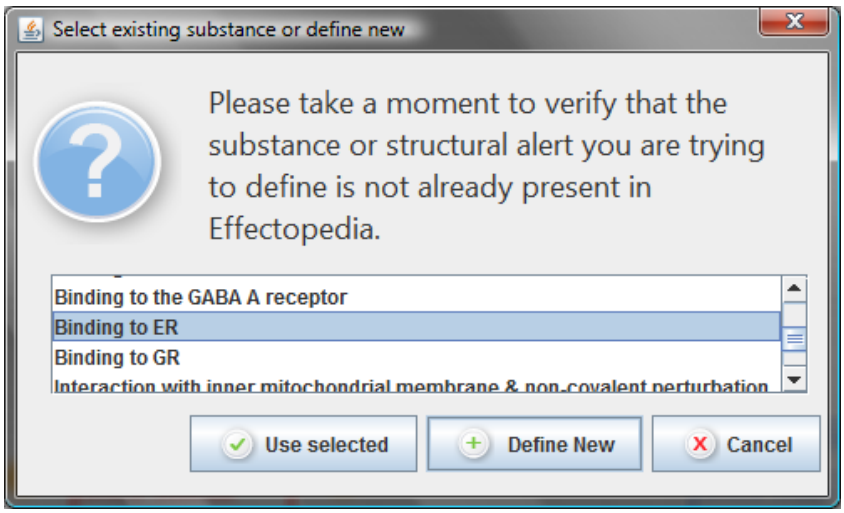
3. Add qualitative information

Once you have build the part or the whole pathway structure you can start editing the newly created pathway elements. You can double click on the element you wish to define or edit. If the element is still generic (no user information is added for it besides coordinates and linkage) and there are previously defined elements in Effectopedia from the same type in the same location warning dialog appears. For example if you click on the chemical structure from step 2. of this tutorial the following dialog appears:



This dialog helps you locate any existing chemical structure that is already defined in Effectopedia. Alternatively in future versions you can use it as a search query to look for the chemical information in external databases. If you have located the chemical you select it from the list and click on "Use selected" if your chemical is not in the list you can click define new. For the purposes of this tutorial select Octylphenol and click "Use selected"

Double click on the molecular initiating event connected to the Octylphenol. New dialog shows asking to verify if the molecular initiating event you are trying to define does not already exists. Please note that only MIE with the same coordinates as the current generic MIE are listed.



Select Binding to ER and click on "Use selected" button. With this all previously entered information about the MIE binding to ER is added to your new pathway.

Move the cursor over the next downstream effect located in the (cellular, mixed) segment and double click on it. This time when the warning dialog shows up click on Define new. This will load the effect editor. Add name to your new effect - this will transform the generic effect object to actual MIE object which can be searched and traced. You can also choose to add some description and references.

To return back to the viewer select View tab located in the upper part of the interface just under the authentication panel.

Go to next step: Add quantitative information or back to Build pathway structure.

4. Add quantitative information

So far in this tutorial all links are hypothetical indicated by the symbol "H" in their icons. Links in Effectopedia provide a place where the causality of the linked elements is defined. Here you can add

both circumstantial evidences and quantitative evidences based on experimental results. For both types of evidences you can also supply literature references.

Continuing with the sample pathway created from the previous step of this tutorial double click on the first link between Octylphenol and Binding to ER. The editor for links from chemical substance to MIE is loaded. Type the name of your link. Next you can change the link type to dose response and provide some data points describing the curve. You can also add the literature references that describe in further detail the experimental conditions under which data was obtained. For the purpose of this tutorial you can add arbitrary fictitious information.

Return back on the viewer by clicking on the View tab.

Please note that the icon of the first link between Octylphenol and Binding to ER is no longer H (for hypothetical) but instead shows a S shaped curve symbolizing the dose response type of link.

Double click on the link connecting Binding to ER to the next cellular effect. Now the editor for link between two effects is loaded. Here again you should start with naming your link. You can choose "Proportional" link type.

Return back to the viewer to see that the icon of the link you have just edited changed to a line - indicating linear type of relationship.

You can go to the last step: Publish your contribution of this tutorial or back to the previous step Add quantitative information.

5. Publish your contribution

The last step of your work is to publish your contribution. For this purpose it it highly recommended that you are signed in.
For the training purposes special account is available in Effectopedia which contributions are never stored into the system but still allows to demonstrate all features available for registered users. The account username is "enthusiast@effectopedia.org" and the password is "inexperienced". Please use this username and password to sign in into Effectopedia.

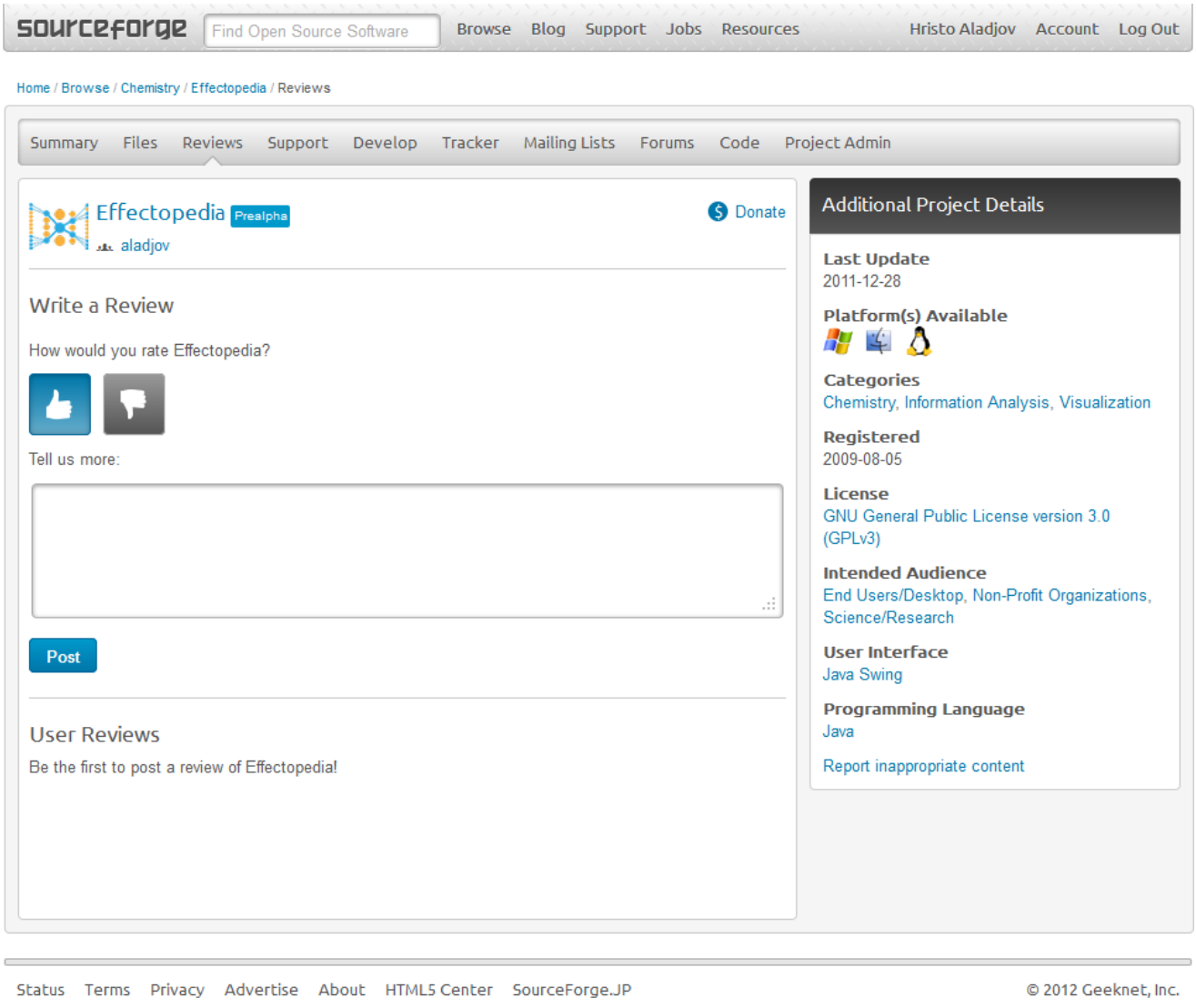
All you need to do now is to press the publish button. In case there are conflicting edits you can use the conflict changes editor to resolve them.

Browse the Effectopedia revision history

Effectopedia Revision history in currently in pre-alpha stages of development and is provided as a glimpse into an important future feature of Effectopedia application. To real more pleas refer to revision history interface.

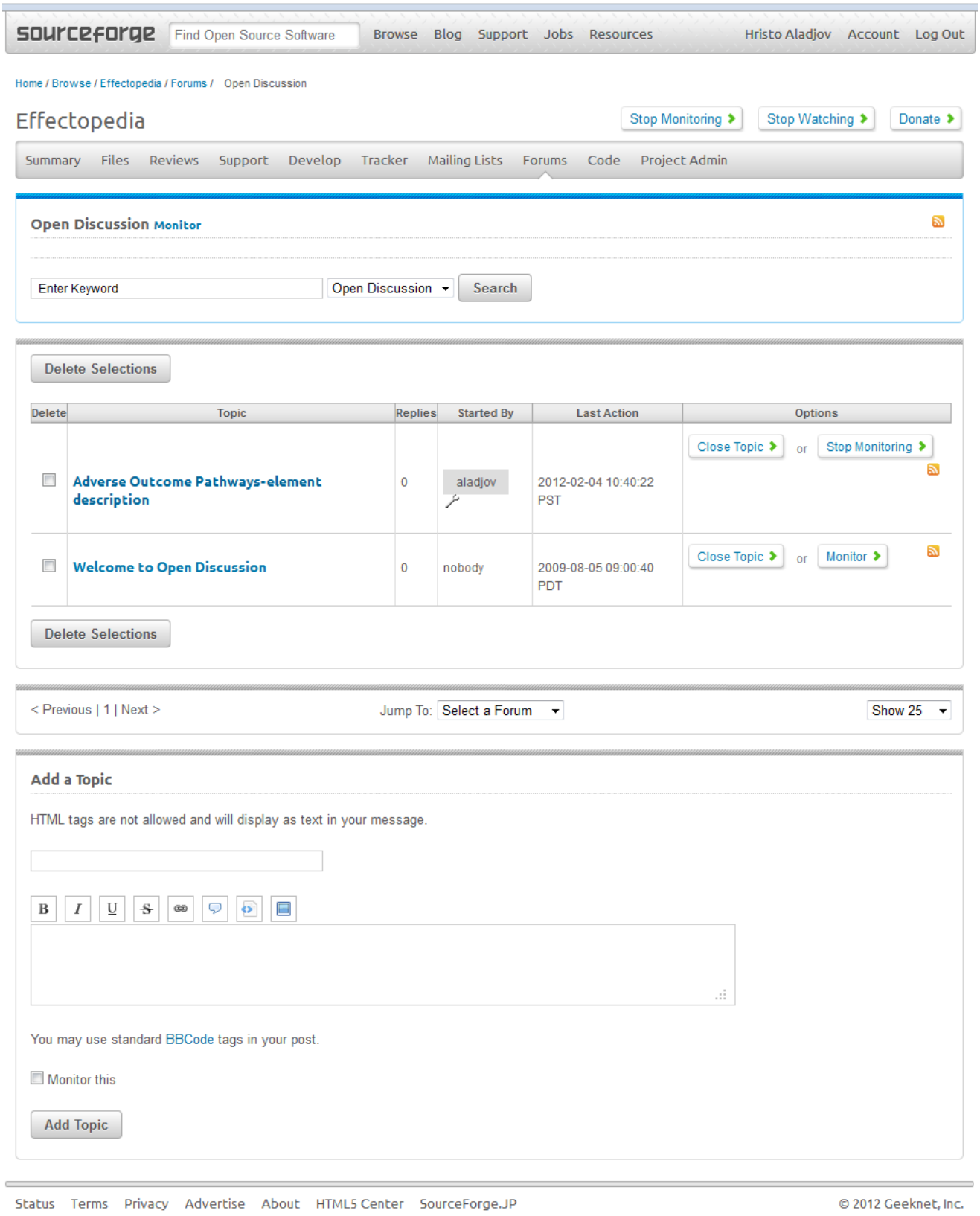
Spread the word by writing a review about the Effectopedia Beta version

Use SourceForge Effectopedia project page to rate your experience with Effectopedia. If you are familiar with the Effectopedia Beta version please share your thoughts in a review that will help others to evaluate if Effectopedia is right application for their needs. Please note that you do not need to register or login in sourceforge.net to rate your experience, but you need to do it if you wold like to post a review. SourceForge makes authentication easy by supporting a list of providers that you can use to login.



Comment on current features of Effectopedia using the Open Discussion Forum

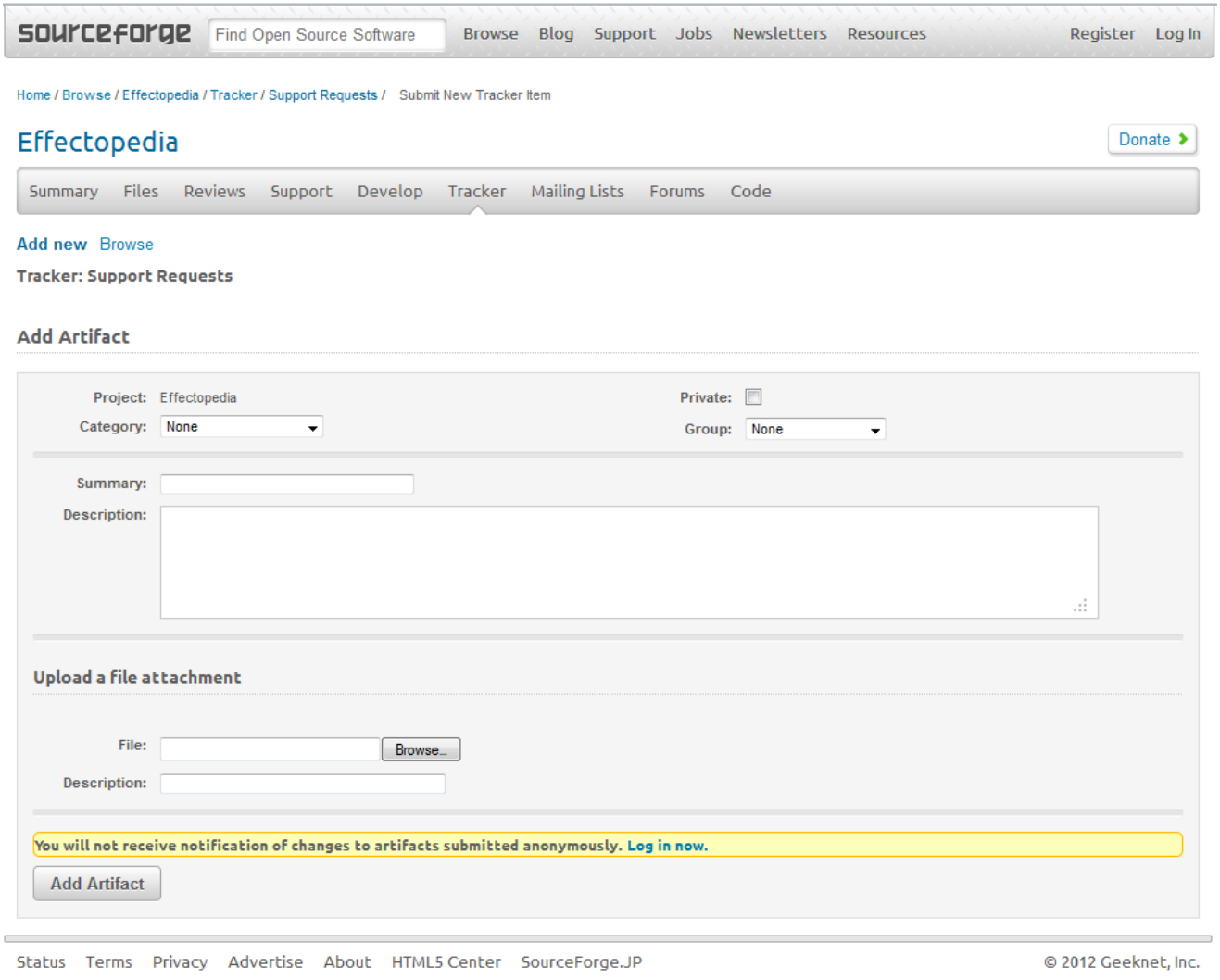
Currently Effectopedia Open Discussion Forum forum is hosted on the sourceforge.net repository. In order to make any posts you need to login into sourceforge web site using some of your existing authentication providers or create / sign in in your SourceForge user account. The discussion forum provides all standard capabilities - to search, browse and add topics and comments.



Submit support requests

Use SourceForge support request system to ask for help when performing specific task with Effectopedia. The two predefined categories are installation and registration issues, but feel free to post "how to" questions in this system. In order to submit a support request:

1. Category which best describes the nature of your request
2. Effectopedia version you are using in the Group field
3. Write a concise description of your need in the Summary field
4. Add clarifying details in the Description.
5. Attach files / screen shots that might be helpful in solving the problem
6. Submit artifact by clicking on the Add Artifact button.

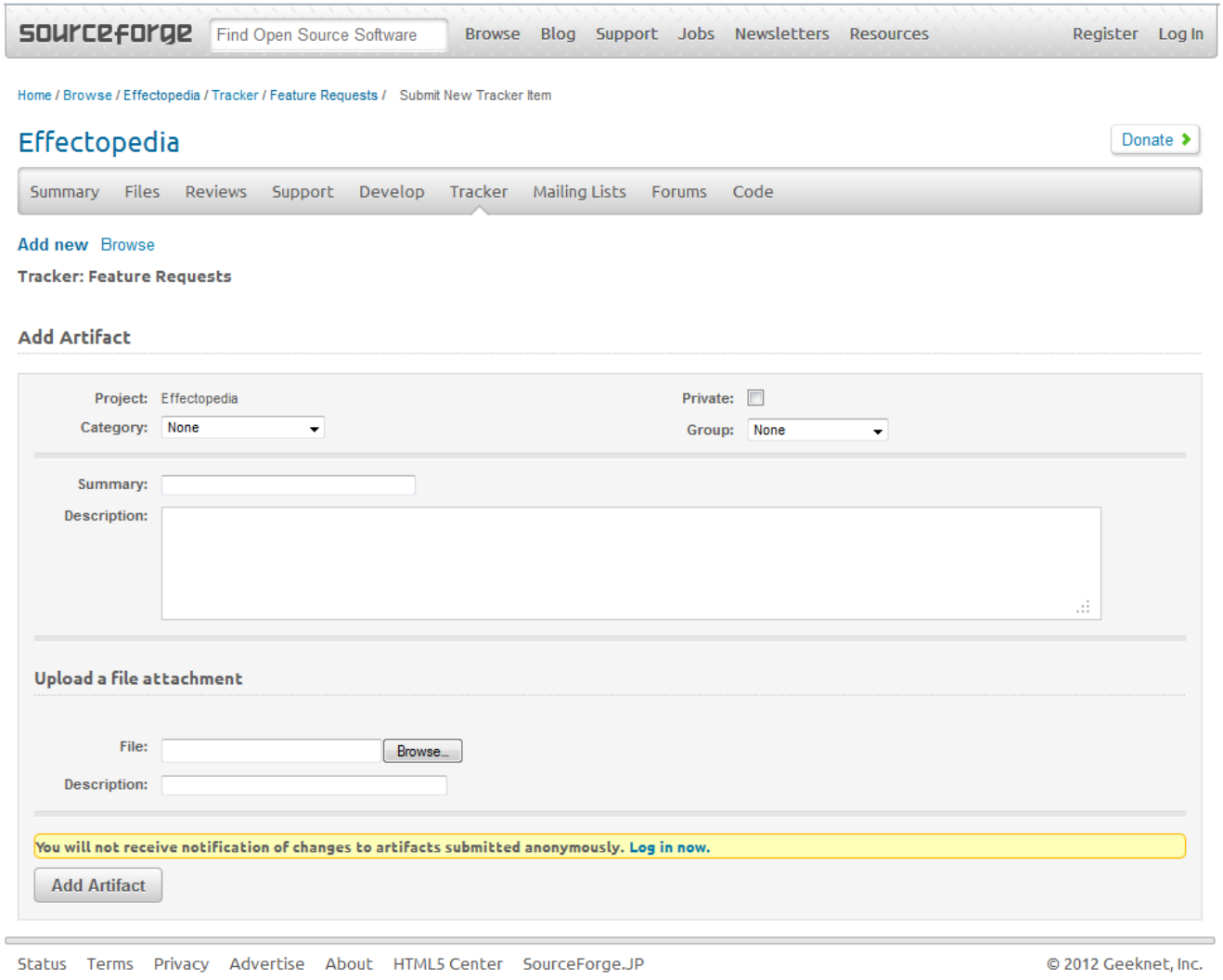


If you choose to post your support request anonymously you want be able to receive direct response from the assigned technician.

Submit ideas and suggestions about Effectopedia

Use SourceForge feature request system to suggest features might be useful to you or the wider Effectopedia community. Sourceforge has a unified tracking system which makes the reporting of bugs and submission of features and support request very similar. In order to submit a feature request you need to:

1. Specify the category which best describes the nature of your request
2. Effectopedia version you are using in the Group field
3. Write a concise description of your need in the Summary field
4. Add clarifying details in the Description.
5. Attach files / sketches that might be helpful in clarifying your idea
6. Submit artifact by clicking on the Add Artifact button.

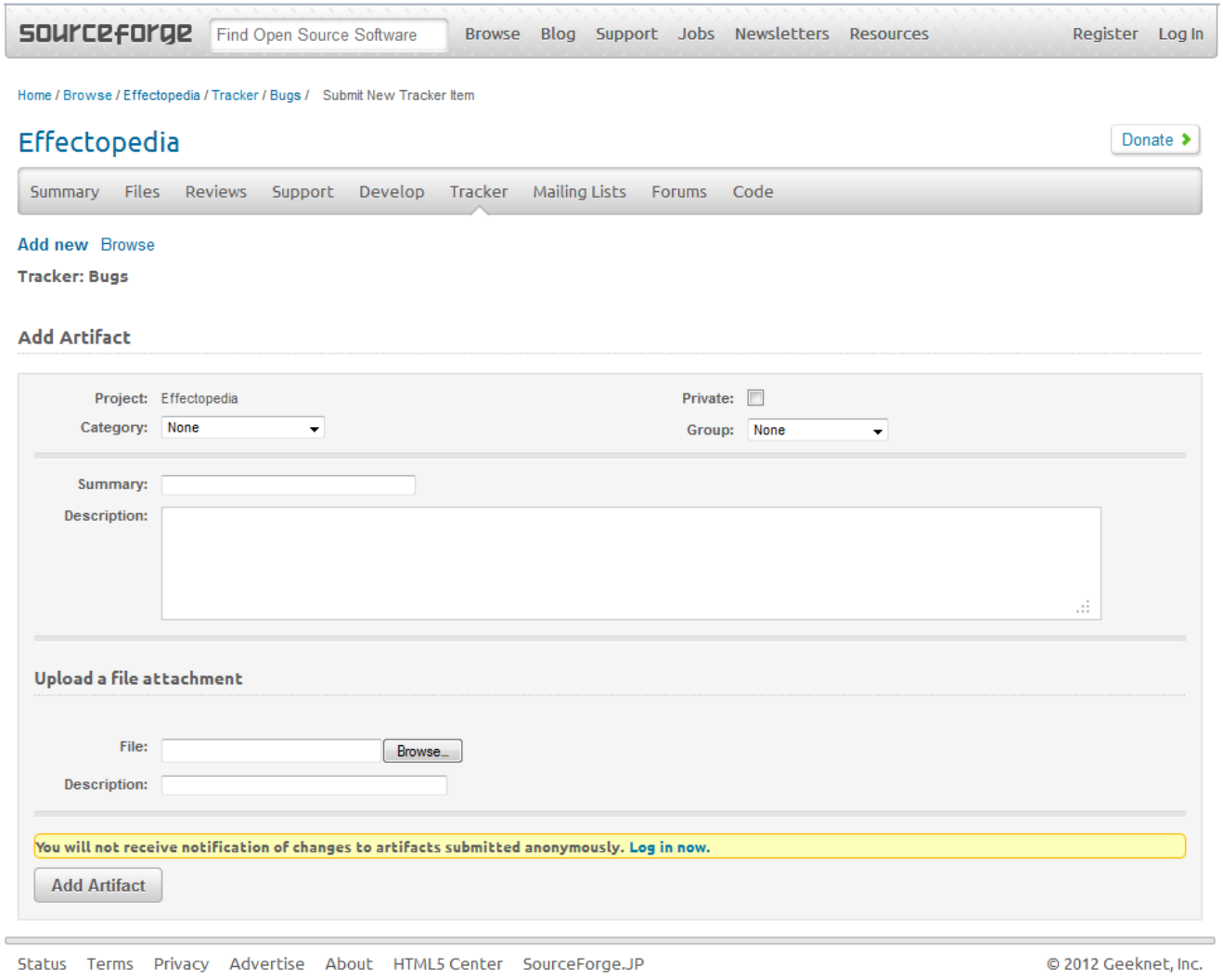


If you choose to post your feature request anonymously you want be able to receive direct response from the project manager.

Submit a bug report and track the progress of its resolving

Use SourceForge bug tracking system to report problems you have encountered in your work with Effectopedia. In order to submit a bug please specify:

1. Category which best describes where the problem occurs
2. Effectopedia version you are using in the Group field
3. Write a concise description of the bug in the Summary field
4. Add clarifying details and describe if the problem occurs always after particular sequence of actions or work with specific data entries.
5. Attach files / screen shots that might be helpful in solving the problem
6. Submit artifact by clicking on the Add Artifact button.



If you choose to post your bug anonymously you wan be able to receive notifications on the progress of its resolving. Please consider registering or login in Sourceforge using some of the supported

authentication providers since bugs will be assigned to a developer's team member and you will be able to follow up the resolving process with him.

Load Locally Stored Files

From the welcome page select "Contribute a new case study or adverse outcome pathway" option to load the pathway viewer interface. From the pathway viewer interface the command toolbar can be accessed. Select file open button  . File open dialog could be used to locate and open the file of interest. The default extension for Effectopedia XML encoded adverse outcome pathways files is "aop" for plain text documents and "aopz" for archived (zipped) documents. Before the official release of Effectopedia the file format is subject to change and no backward compatibility is guaranteed. Loading files created with different version of Effectopedia application could lead to unpredictable results. Once the file format is stabilized backward compatibility will be guaranteed.

Save to local file

Use the file save  button from the command toolbar to save the currently active data source in XML encoded local file. You can manually type the extension "aop" to save file as plain text documents and "aopz" for saving the file as archived (zipped) document. Before the official release of Effectopedia the file format is subject to change and no backward compatibility is guaranteed. Loading files created with different version of Effectopedia application could lead to unpredictable results. Once the file format is stabilized backward compatibility will be guaranteed.

Adverse Biological Effect

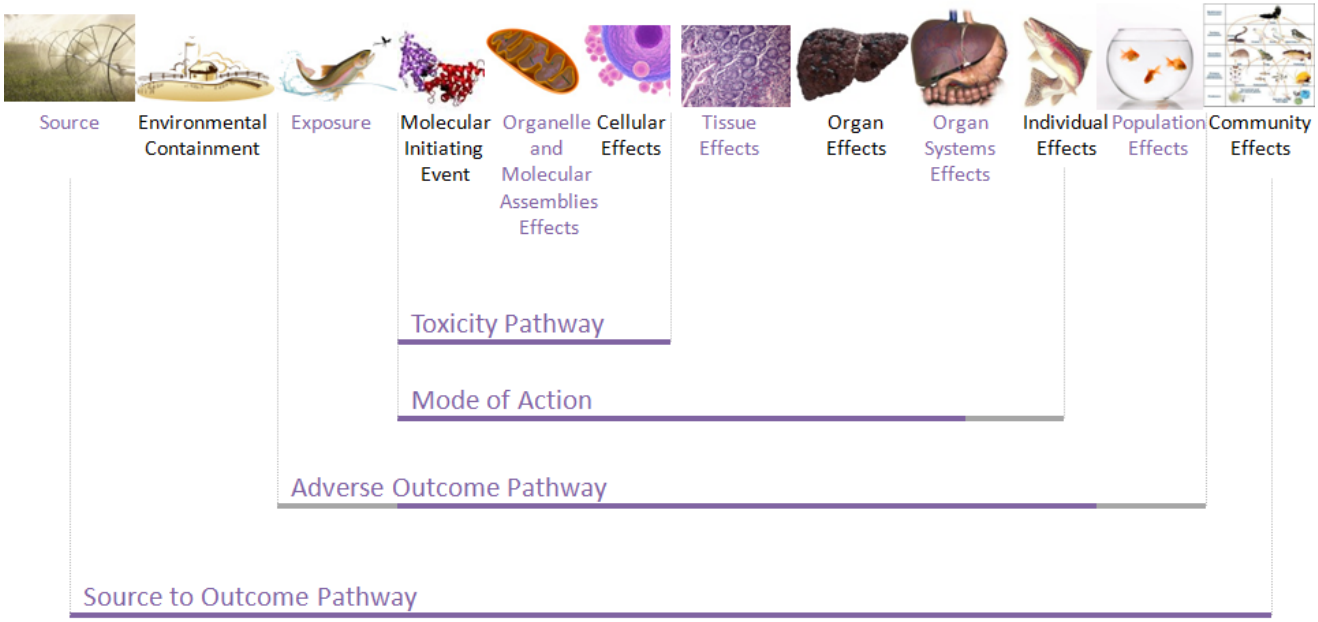
Adverse Biological Effects are important observable changes in a biological system or subsystem resulting from an experimental perturbation which, if continued, would be expected to contribute to dysfunction and disease progression at high levels of biological organization.

Adverse Outcome

Adverse Outcomes define the primary context for a risk assessment and groups the measurable adverse effects according to their contribution to the risks of short-term lethality, impaired development, impaired reproduction, carcinogenicity and progression of other long-term diseases.

Adverse Outcome Pathways

The adverse outcome pathways (AOP) describes the molecular interactions of a chemical with biological systems and the biological response models that document how molecular effects lead to adverse effects many levels of biological organization. The user is referred to Ankley et al. (2009) and Schultz et al (2010) for discussion of AOPs. In the context of predictive models for hazard identification, QSAR models are used to predict the molecular interactions of chemicals whereas the biological response models in AOPs are used to predict the progression of biological effects in the cell, tissue, organ, individual and population levels.



Adapted from Kevin Crofton 2010, OECD AOP Meeting Definitions .

Case Study

Case Study is a more comprehensive assessment of the adverse effects and biological pathways caused by a specific chemical or resulting from a common biological dysfunction caused by a group of similar chemicals. A Case Study includes existing hazard assessment summaries as well as book chapters and other critical reviews of the scientific literature.

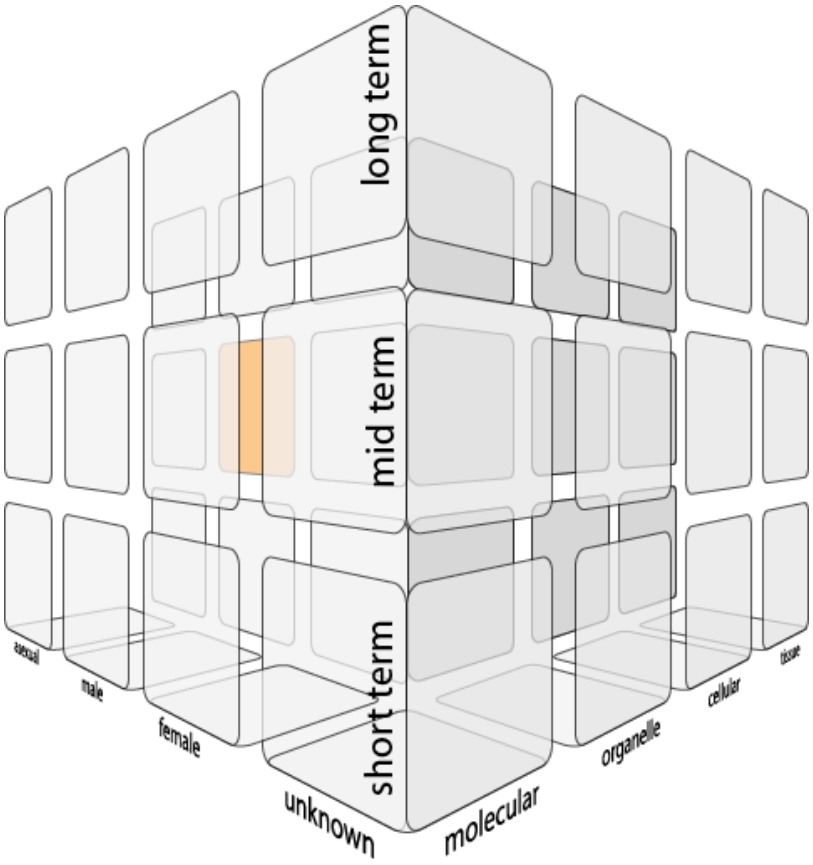
Chemical Substance

A chemical substance is the chemical used in an experiment to measure effects at any level of biological organization and is distinguished from case studies in that it can be used to document a single experiment as opposed to a consensus of knowledge and understanding of mechanisms.

Effectopedia enables the AOP to include important metabolic activation steps so that inactive parent chemicals can be related to the appropriate molecular effects through documented biotransformation.

Context Dimensions

In Effectopedia each important factor that specifies when and under what conditions certain effect can be observed are regarded as dimension in Effectopedia pathway space and defines the context in which the effect is described. Example of context dimensions are life stage, species, gender, time form exposure, etc. The list of dimensions is not fixed and can be expanded upon user requests and trough planned interface in the future releases of Effectopedia. Context dimensions also help locating similar effects and avoid the duplication of entries.



Default and Generic Objects

The concepts of Default and Generic objects were introduced to Effectopedia in order to provide a place-holder data entities for the user interface and eliminate the need for storing non user generated information more than once in the system.

Default object is a data structure with predefined values for all fields that does not contain any user contributed knowledge. Default objects are not indexed by the search system and could not be found by search queries. Default objects are special case of Effectopedia objects and can be nested in hierarchical structures. For example Each effect contains Description, Context and References objects which could remain default until user add any content to them even in case they are part of object which is no longer default.

Generic objects are created in the pathway viewer and placed in a specific location. Generic objects have two coordinates of the location automatically assigned to them and therefore are no longer default objects. While in their generic state these objects can be replaced with other compatible objects in the same location (usually by clicking on the object while selected in the pathway viewer). Generic objects are stored in Effectopedia but they can be only retrieved from context dimensional search by their coordinates.

Effectopedia Objects and Properties

Effectopedia objects and object properties are the smallest abstract building blocks with which all knowledge in Effectopedia is encoded. Each object property represents a single value of specific type, describing the object in some capacity (e.g. Title is a property of Molecular Initiating Event Object). Effectopedia objects can contain properties and other objects.

All changes to Effectopedia objects and properties are tracked by the revision history system and and all previous versions remain stored. This allows detailed information on who and when certain contribution was made as well as provide a mean for easy retrieval of old versions.

Search subsystem is also tracking the changes to the Effectopedia objects and properties updating search indices so these changes become visible immediately in the local system and to other users after publishing.

Hazard Assessment Endpoint

There are thousands of observable biological effects in the in vitro and in vivo assays use in toxicology. However, a smaller subset of biological endpoints are suitable as endpoints for modeling purposes and a much smaller number of biological effects have been adopted a regulatory hazard assessment endpoints. The primary reason to highlight the hazard assessment endpoints is to orient the delineation of adverse outcome pathways to those endpoints most useful to hazard assessment.

Link between Substance and MIE

The link between a chemical and MIE is used to quantify the impact of a chemical structure on a specific receptor or functioning biological system. The linkage may be defined in terms of a binding affinity or a dose-response curve for the molecular interaction. The user is reminded that a single chemical many have links with multiple MIEs and that their may be many other chemicals with a link to a specific MIE.

Link between two Biological Effects

The link between two biological effects is a response-response model and quantitative relationships may not be available in the literature. The user can qualitatively link two effects by choosing the shape of the response-response curves and further quantify it with a general threshold value for downstream effects. In many cases, a series of intermediate effects can be hard-wired by making the link coefficient 1.0, which simply means that there is a cascade of effects.

Metabolic Activation Link

The metabolic activation link provides an opportunity to document knowledge regarding the metabolic activation of a specific chemical in a specific organism. When a putative metabolite is expected to be responsible for the MIE, this link allows the user to document that the chemical can be transformed to the activated metabolite along with tissue specificity, if known, for the activation.

Molecular Initiating Event

Chemicals to not affect populations or individuals or organs or cells. Chemicals interact at the molecular level with biological systems and some of those interactions disrupt the normal function. The disrupting interaction of chemicals with a biological system produces a molecular initiating event (MIE) which causes observable biological responses that make up the adverse outcome pathway.

Reactive Substance

Although chemical reactivity spans a wide spectrum of chemical interactions, reactive chemicals in Effectopedia are regarded a those capable of forming covalent bonds with DNA, proteins and membranes. Because potency and selectivity of chemicals depend on binding affinity, metabolic conversion of a chemical to a reactive metabolite is called metabolic activation and results in much different toxicological behaviour than the parent chemical.

Structural Alert

A structural alert in a chemical substructure or property which is considered essential for chemicals to exhibit specific behavior or effects. Structural alerts are an integral part of QSAR which allows specific molecular initiating events to be associated with many discrete chemicals which share an important substructure.

Test

A test in Effectopedia is defined as an establish OECD test guideline or referenced experimental procedure which can be documented in the scientific literature.

Introduction to editors

Effectopedia editors share many sub-components which provide unified interface for editing particular types of contained objects or properties. For example there is only one type Reference manager which is loaded as a part of all Link, Effect and Pathway editors. The same is true for the Description component. These sub-components are described in the Editor Components section of this help and referred to from the specialized editors.

Context sensitive help system provides more targeted information for each component under the cursor.

Creating a new account

If you are new to Effectopedia and would like to create an account with us you can:

1. Select the Sign-in link in the upper right corner of the Effectopedia application
2. From the right panel on the sign in form select New Account Signup
3. Fill all required fields shown in bold in the form below
4. Click on create new account.

A. Upon successful registration your username should show up in the Authentication line at the top of the Effectopedia application.

B. Next time you sing in use your e-mail address as a user name and your password.

Signing in and out of the system

It is highly recommended to sign-in before making any contributions to Effectopedia. This is the only way you can take credit for your work and get notified when relevant changes or connections are made. Once registered you can still choose to remain anonymous by choosing "anonymous" display name. In order to be able to login into the system you have to have internet connection

1. Select the Sign-in link in the upper right corner of the Effectopedia application
2. Type your e-mail address as user name and your password.
3. Click on the sign in button.
4. After successful login the default welcome page is loaded again and your chosen display name is shown in the upper right corner
5. Once you are done working with the system you can click on the logout link next to your name into the authentication panel on the top of the Effectopedia Application

Using external service providers

The support of external authentication is currently in its alpha stage of development. The main goal of this system is to minimize the efforts for registering into Effectopedia system by pooling out information from your existing registrations. Effectopedia will limit the amount of information

retrieved from the external service provides to the following fields **name** and **family name**, **e-mail**. A password will be generated which you can use for future logins along with your e-mail address. Currently supported authentication providers are: **Google, Yahoo, LinkedIn, Microsoft Live, Facebook, Twitter, OpenID**

To use an external authentication:

1. Select the Sign-in link in the upper right corner of the Effectopedia application
2. From the right panel on the sign in form select Desired authentication provider
3. The default web browser will be launched and provider authentication form loaded
4. After successful login into the chosen provider - generated user profile is displayed.
5. Use the displayed e-mail address and generated password for future logins into the system.

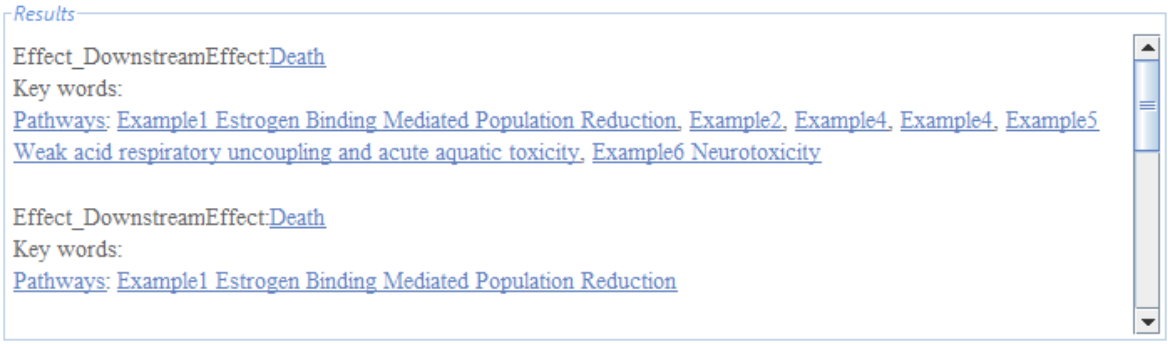
Build a search query

Please refer to
- building a search query to find a chemical or case study or to
- building a search query to find AOPs or Effects

sections of the help depending on what are you looking for. You can also use the context sensitive help system to guide you on each step of your query building. Once the query is built click on the search button and use the search results.

Use search results

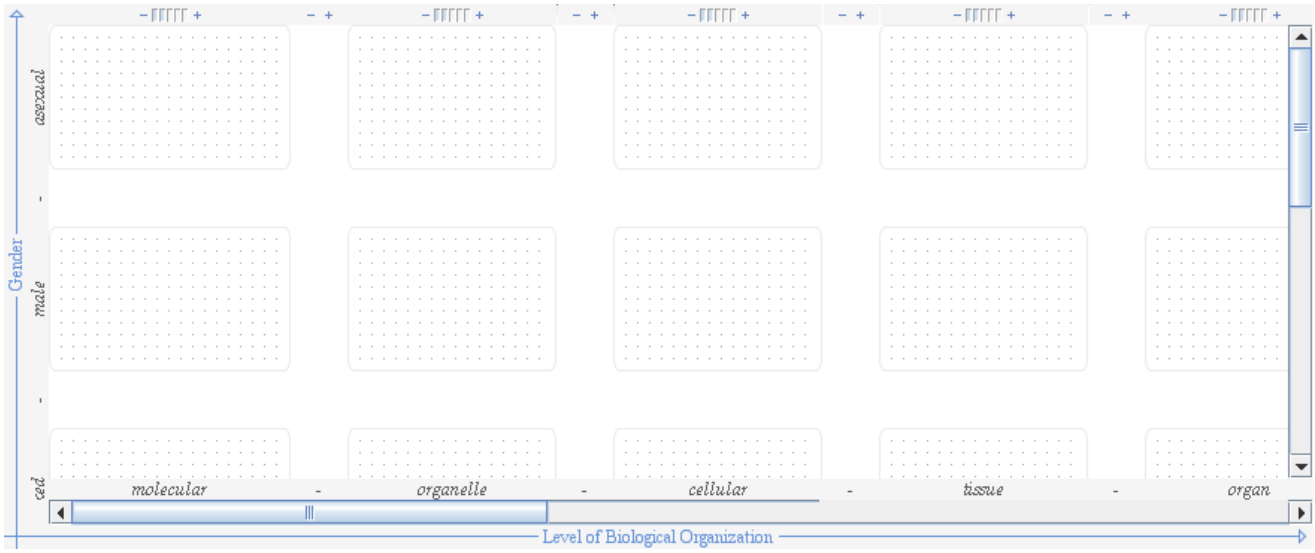
Search results are displayed in the results component below the search button. The results can contain different types of objects which behave differently when loaded into the pathway viewer. For example if we search for the title "death" several results are shown. The first one shows that downstream effect with caption Death was found. You can load the first pathway containing this effect by clicking on the name of the effect. When single effect is loaded it is selected and pathway viewer is positioned so it becomes visible. There are no keywords associated with this effect so nothing is displayed on the next line. On the last line there is a list of all pathways of which this effect is part of. You can choose to load individual pathway by clicking on the name of the pathway or choose to load all pathways if you click on the Pathways: link at the beginning of the list.



Pathway Space Viewer

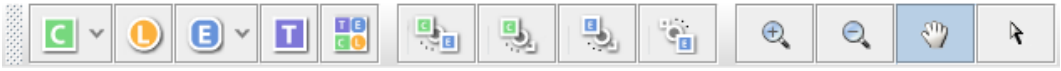
Pathway Space Viewer shows a two dimensional projection of the Efectopedia Pathways space. The two dimensions currently displayed are specified in the vertical and horizontal axis on the right and bottom of the viewer respectively. Each dimension can be switched to another one by right clicking on the axis. Different types of axis exist. Some can have fixed number of ordered categories shown in the axis labels, others can be continuous or does not have a fixed set of values.

Pathways space is divided into segments (represented by gray rectangle with dotted fill). These segments separate the categories when certain axis have categorical values in such a way that any given segment contain only one of the categories. For example Gender and Level of Biological Organization are both categorical axis so the segment coordinates provide the type of elements it contains (e.g. MIE that are defined only at molecular level for males). When axis are non categorical and can have continuous ordered values then the objects are sorted according to their coordinates.



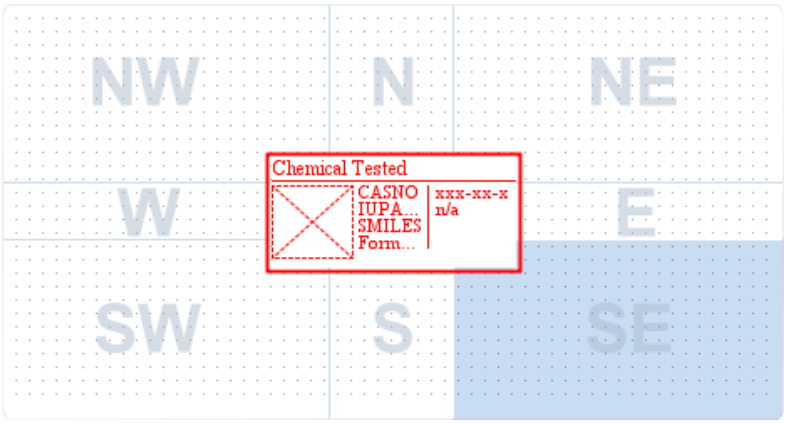
Pathway Space Viewer Modes

The mode toolbar



can be formally divided into three sections: modes for creation single pathway elements, wizard modes and control modes.

First five buttons on the mode toolbar are used to create a single pathway element at specific location. When the pathway space viewer interface is in any of the element placement modes the segments show the active region where the next element will be inserted. When the segment is empty the whole segment is highlighted indicating that the new object will be placed in the center of the segment. When there is some object in the segment the user can choose where relative to this object wants to insert the new object (indicated by the world directions on the figure below). Moving the mouse to the center of the region can be used to change or select the current object under the cursor without inserting a new element.



First set of buttons turn on the mode for placing chemical substances or structural alerts. While you are in this mode you can create as many chemical substance as you like. Please note that chemical substances can not be put in arbitrary location on the screen but are limited to the first segment only. When you click in the center of an empty segment or in some of the named regions above new generic object is created with the currently selected type. To change the type of the object click once more over it while the whole segment is highlighted. In this process you can cycle trough all the substance type objects chemical substance, metabolite, structural alert.

The link button activates link creation mode.In this mode you can create all types of link in any sequence. You can select the cause pathway element first, then click on an empty space to place the link, and then click on the second pathway element. You can start with placing the link first and then selecting the two elements to connect.

The effect set of buttons allows you to place molecular initiating events, adverse biological effects, hazard assessment endpoint and adverse outcome. The newly placed elements are kept generic until some of their properties is edited. Similar to chemicals substances you can change the effect type cycling through all effect types by clicking in the central area of the element (indicated by

the surrounding highlight). Effects can be placed only inside of segments since they need to have context defined.

New test mode can be activated by pressing the test  button. Test can be placed where effects can.

The CLET button  is provided as a universal mode which can be used to place all of the above elements. In this mode the system tries to guess what the next element will be and change the type accordingly. Step by step demonstration on how to use the CLET mode is provided in the building a pathway structure section of the help. The CLET mode is very suitable for creating branched structures of the pathways or case studies.

For efficient creation of long linear segments of pathways or case studies are supplied the four wizard modes. The difference between modes is in the start and end element which is used in the mode. The pathway wizard  allows you to build pathway starting from a chemical and finishing with adverse outcome. The direction you choose to build the pathway (from the chemical to outcome or the opposite) determines where the most of the linear segment of the pathway will lay. Once you have created the pathway and the pathway is still selected you can delete elements from it without loosing the connectivity. The modes upstream effect wizard  and downstream effect wizard  allow you to build respectively upstream and downstream linear segments terminating at effects. If you would like to build upstream segment terminating at chemical substance you can use  .

The last set of modes allow different control functions:

The zoom in and out buttons can be used to zoom in and out the pathway space. Different level of details from the pathway element descriptions are shown in the different zoom levels. If you hold control key you can click on a single pathway element to zoom in and only this element.

The drag mode  allows the pathway space to be scrolled. It also allows objects to be dragged within the ranges of the current fragment.

Edit mode  allows selection of multiple objects by creating a selection rectangle and dragging the mouse. Holding the shift key before selecting a single pathway element until a second pathway element is selected allows all connected on the path between the two clicked objects to be selected. Holding the Ctrl key allows to include and exclude individual objects from selection. Clicking in the space not occupied by any object allows all objects to be deselected. To select all objects you can use Ctlr+A keys. Once the objects are selected you can delete them from the current view. Objects are deleted from the view only and continue to exist.

Pathway Space Viewer Commands

The commands toolbar

is currently located in the main pathway view window. This toolbar provides access to XML file loading and saving dialogs as well as the remote publishing feature.

Press  button to open existing Effectopedia encoded XML file. File open dialog could be used to locate and open the file of interest. The default extension for Effectopedia XML encoded adverse outcome pathways files is "aop" for plain text documents and "aopz" for archived (zipped) documents.

Use  button to save the currently active data source in XML encoded local file. You can manually type the extension "aop" to save file as plain text documents and "aopz" for saving the file as archived (zipped) document.

Use the down arrow next to save file icon to reveal the publish button  and press it to publish the currently active data source in the remote storage location. By default current data source is the centralized Effectopedia database and the default remote server for publishing is effectpedia.org. In the current version file is transported in the form of archived "aopz" document and saved by the version control system on the server with appropriate name.

Case study editor

The case study editor is still not implemented in the current version of Effectopedia. The editor interface will be very similar to the pathway editor interface but will have one additional item of associated pathways. Other possible auditions are third party case study identification numbers.

Chemical Substance Editor

The chemical substance editor is still in its initial stages of its development and provides only the very basic interface to add chemical descriptions into the system. In future versions of Effectopedia chemical editor is envisioned to be highly automated and retrieve virtually all relevant information via quick auto-complete search from various Internet accessible repositories.

The interface of the chemical editor is shown on the screen capture below. It consist of four major panels.

First is two dimensional depiction of the chemical structure. Currently you can add link to internet location of a image file containing the structure. Official Beta release will include an automated

service for generating the image based on the provided smiles. Future versions might also include some chemical structure drawing tools.

Second panel includes basic chemical information. This panel will serve a dual purpose in the official Beta version as a search fields and once an appropriate match is found all remaining fields will be auto completed.

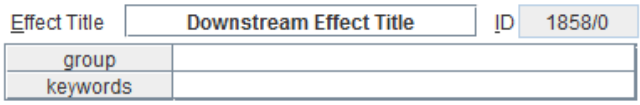
Chemical properties panel currently contains some very basic properties of the chemical structure. Future versions will have connections with third party services for calculation of important parameters as well as retrieving measured data.

The synonym column contains alternative common names of the chemical. This names will be further added as an option for a search field in queries.

Effect editor components

All effects Adverse Biological Effects, Hazard Assessment Endpoints, Adverse Outcomes and Molecular Initiating Events are all currently edited in a single customized editor. This editor contains the following interface components: Effect header information, description, context, associated pathways and references. From those components only the effect header is unique for the effect editor and will be described here the remaining components are described in the editor components section of this help.

Effect header contains information about the effect title, internal and external ids, keywords and groups.



Use the effect title to describe the effect in concise manner. In future versions of Effectopedia this field will have a taxonomic underlying structure to avoid arbitrary naming of the effects (or duplicating effects in Effectopedia under different names)

The first number in the effect ID shows the internal memory unique identifier of the effect. If the effect was loaded from external data source the second number shows the unique identifier in this data source. This information is provided for technical support purposes.

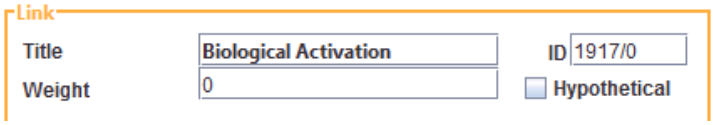
Some effects can be associated with groups containing similar effects with respect to a specific hazard category, higher levels of organization, biological classifications, etc. In the group field provide comma separated list of groups to which this effect belongs to. In future versions of Effectopedia auto-complete selection of existing groups will be added to this field.

Keywords provides a place to list of keywords by which this effect can be categorized and found in search queries.

Metabolic Activation Link

The process of metabolic activation is represented by a single link which can be edited in the Metabolic activation link eidor.This
editor contains the following interface components: link header information, description,
enzyme system, associated pathways and references. From those components only the link header and enzyme system are
unique for the link editor and will be described in the text below. The remaining components are described in the editor components section of this help.

Link header contains information about the link title, internal and external ids, weight and hypothetical flag.



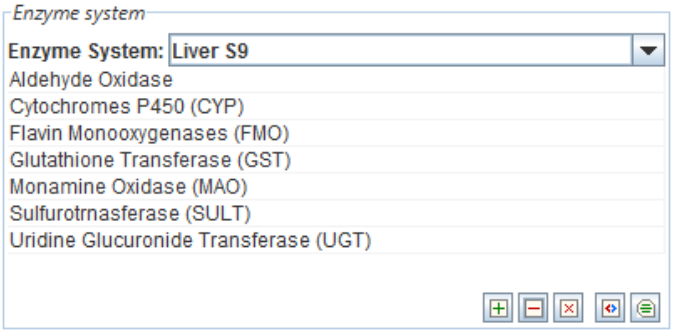
Use the link title to describe the link in concise manner.In future versions of Effectopedia this field will have a taxonomic underlying structure to avoid arbitrary naming of the links.

The first number in the link ID shows the internal memory unique identifier of the effect. If the link was loaded from external data source the second number shows the unique identifier in this data source. This information is provided for technical support purposes.

Weight is a field reserved for a future use in the vulnerability analyses.

Hypothetical flag - this flag is automatically maintained depending on the chosen link type. It is common property of all link objects and is used when determining the display icon of the link in the pathway space editor.

Enzyme system specifies under what conditions the metabolic transformation occurs. This could be used to define different metabolites coming from the same parent chemicals in different organisms and enzymatic systems. To define the enzyme system please choose one from the list or define a new one press ⊞ button. Click on the last row containing your new enzyme. You can use the auto complete drop down list of existing enzymes. In the current pre-release version only partial list is supplied, but soon it will be replaced with remotely accessed third party based biological ontology. To remove the selected enzyme from the list press ⊟ or to remove all listed enzymes press ⊠. .

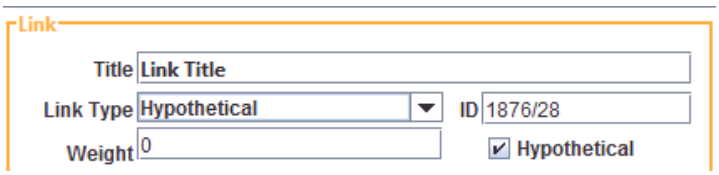


To define a new enzyme system or edit existing one you can use the toolbar at the bottom of the Enzyme system interface component. When you click

Substance to MIE Link Editor

Substance to MIE link editor has a dynamic structure of its interface components depending on the selected link type. The ever present interface components are: Link header information, description, associated pathways and references. The dynamic component of the interface is the dose-response component.
Link header is specific to this types of links and along with all dynamic component will be described in the text below. All the remaining components are described in the editor components section of this help.

Link header contains information about the link title, link type, internal and external ids, weight and hypothetical flag.



Use the link title to describe the link in concise manner.In future versions of Effectopedia this field will have a taxonomic underlying structure to avoid arbitrary naming of the links.

The first number in the link ID shows the internal memory unique identifier of the effect. If the link was loaded from external data source the second number shows the unique identifier in this data source. This information is provided for technical support purposes.

Link type describes the quantitative nature of the link. Currently the following options are available:
- Hypothetical - link type is unknown or there is no experimental or other evidences to support this link. It is hypothesized form the contributing expert based on his own experience and intuition.
- Dose response - link type can be used to describe nonlinear association between the dose and the magnitude of biological response.

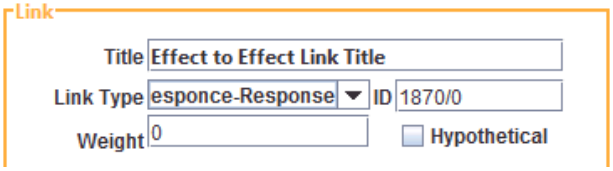
Weight is a field reserved for a future use in the vulnerability analyses.

Hypothetical flag - this flag is automatically maintained depending on the chosen link type. It is common property of all link objects and is used when determining the display icon of the link in the pathway space editor.

Effect to Effect Link Editor

The editor of links that connect two downstream adverse effects has dynamic structure depending on the type of the link. The constant interface components are: Link header information, description, associated pathways and references. The dynamical components of the interface are: threshold level, linear dependency, response-response.
Link header is specific to this types of links and along with all dynamic components will be described in the text below. All the remaining components are described in the editor components section of this help.

Link header contains information about the link title, link type, internal and external ids, weight and hypothetical flag.



Use the link title to describe the link in concise manner.In future versions of Effectopedia this field will have a taxonomic underlying structure to avoid arbitrary naming of the links.

The first number in the link ID shows the internal memory unique identifier of the effect. If the link was loaded from external data source the second number shows the unique identifier in this data source. This information is provided for technical support purposes.

Link type describes the quantitative nature of the link. Currently the following options are available:
- Hypothetical - link type is unknown or there is no experimental or other evidences to support this link. It is hypothesized form the contributing expert based on his own experience and intuition.
- Direct - this link type represents "hardwire" type connection between the two effects. It is equivalent of linear dependency with slope coefficient 1.0 and intersection 0.0
- Threshold - link type provides a threshold value above which the upstream effect starts to cause the downstream effect. Once the threshold is passed the link becomes equivalent to linear dependency with slope coefficient 1.0 and intersection 0.0
- Proportional - link type can be used to describe linear association between the upstream and downstream effect.
- Response response - link type can be used to describe nonlinear association between the upstream and downstream effect.

Weight is a field reserved for a future use in the vulnerability analyses.

Hypothetical flag - this flag is automatically maintained depending on the chosen link type. It is common property of all link objects and is used when determining the display icon of the link in the pathway space editor.

The following interface components show only when particular type of link is selected.

For the threshold type of links Threshold level component showed below appears.

it allows for the user to enter threshold level and response units.

For the proportional link type the Linear dependency component is loaded.

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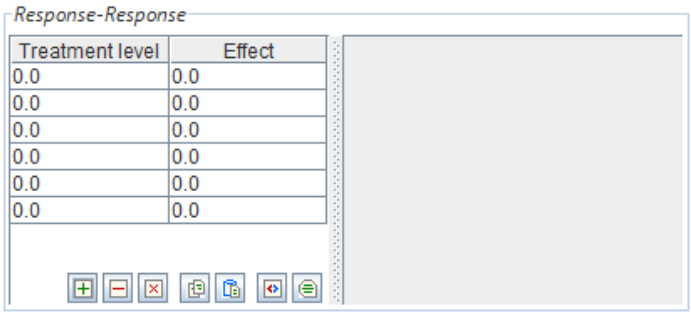
it allows for the user to define the slope and intersection of the linear dependency as well as treatment and response units.

For response response link types the following component is loaded:



it allows the user to enter points form the response response curve. This could be done manually, using ⊞ button to add new point from the curve, ⊟ to remove currently selected data point, ⊠ to remove all points. You can also paste tab delimited data array from external data source (for example excel table)

Test editor

The test editor is in the initial stages of its development and will be further expanded to maintain information about the test protocols and guidelines. Currently test editor cossets of the following interface components: test header, description, context, labs and references. From those components the two components that are unique for the effect editor and will be described in the text below.

Please refer to the editor components section of this help to learn more about the remaining components of the test interface.

Test header contains information about the test title and internal and external ids.

Use the test title to describe the test in concise manner. If the test is standardized use the common name or the test.

The first number in the effect ID shows the internal memory unique identifier of the effect. If the effect was loaded from external data source the second number shows the unique identifier in this data source. This information is provided for technical support purposes.

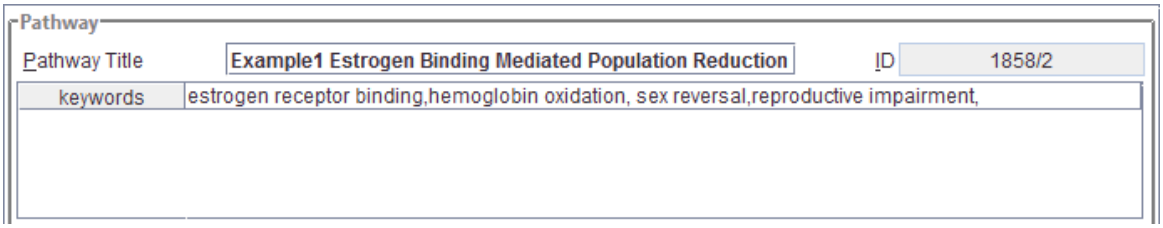
Labs interface provides a place where test labs and companies can advertise their services for performing the described test. Currently basic contact information is maintained. To add a new lab press ⊞ button, to remove selected lab press ⊟ or to remove all listed labs press ⊠.

Pathway Editor

The chemical substance editor is still in its initial stages of its development and provides only the very basic interface to add chemical descriptions into the system. In future versions of Effectopedia chemical editor is envisioned to be highly automated and retrieve virtually all relevant information via quick auto-complete search from various Internet accessible repositories.

Pathway editor contains the following interface components: pathway header information, description and references. From those components only the pathway header is unique for the pathway editor and will be described in the text below. All the remaining components are described in the editor components section of this help.

Pathway header contains information about the effect title, internal and external ids and keywords.



Use the pathway title to describe the pathway in concise manner. Usually this description includes some information about the important molecular initiating events and adverse outcomes associated with this pathway. In future versions of Effectopedia this field will have a taxonomic underlying structure to avoid arbitrary naming of the pathways (or duplicating pathways in Effectopedia under different names)

The first number in the pathway ID shows the internal memory unique identifier of the pathway. If the effect was loaded from external data source the second number shows the unique identifier in this data source. This information is provided for technical support purposes. All Effectopedia objects have unique internal ID which can help in their identification.

Keywords provides a place to list of keywords by which this pathway can be categorized and found in search queries.

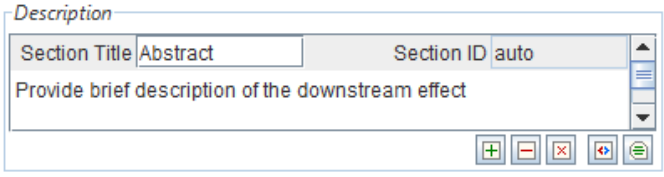
Structural Alert Editor

The structural alert editor is still not implemented in the current version of Effectopedia.

Description editor

Many Effectopedia entities require different forms of description. The future versions of Effectopedia will rely on underlying context and associated biological ontologies to make this description semantic. This will require simple auto completion terms entry form the user. This functionality will be also targeted to cover nano publication requirements. The description sections will also support BBCode HTML tags for formatting and displaying external content.

Currently you can add multiple description sections with titles. To add a new section press ⊞ button, to remove the current description section press ⊟, to remove all description sections click on reset ⊠ button. You can use the discuss button ⇔ to start a discussion on the subject if this description is accurate or in future versions of Effectopedia sing in and initiate a chat on that subject.



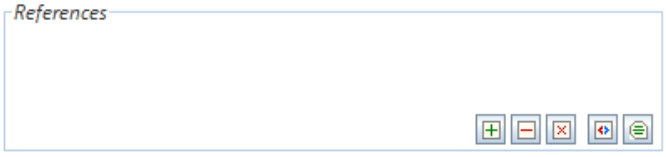
Associated pathways editor

All pathway element component share this associated pathways editor. With the help of this interface all pathways that include the current element can be added. To associate a new pathway with the current element press ⊞ button. A dialog shows providing you a chance to pick among the existing pathways or define a new one. To remove a pathway from the list select the row containing its name and press ⊟ . To remove all pathways click on reset ⊠ button. You can use the discuss button ⊡ to start a discussion on the subject if this pathway element should be associated with given pathway or in future versions of Effectopedia sing in and initiate a chat on that subject.

Reference editor

In the coming beta version of the program the reference manager will support searching in IEEE, PubMed and JStore online repositories for finding and auto retrieving your reference entry. The search will be executed when you start typing in a new reference item. You can start typing name of the authors, titles of the article / book, year of publishing and so on which will narrow down the list of matching publications. Once you are able to see the reference you are looking for in the drop down list you can select it and add it to the reference list. Also pasting bibtex formatted list of references will be supported.

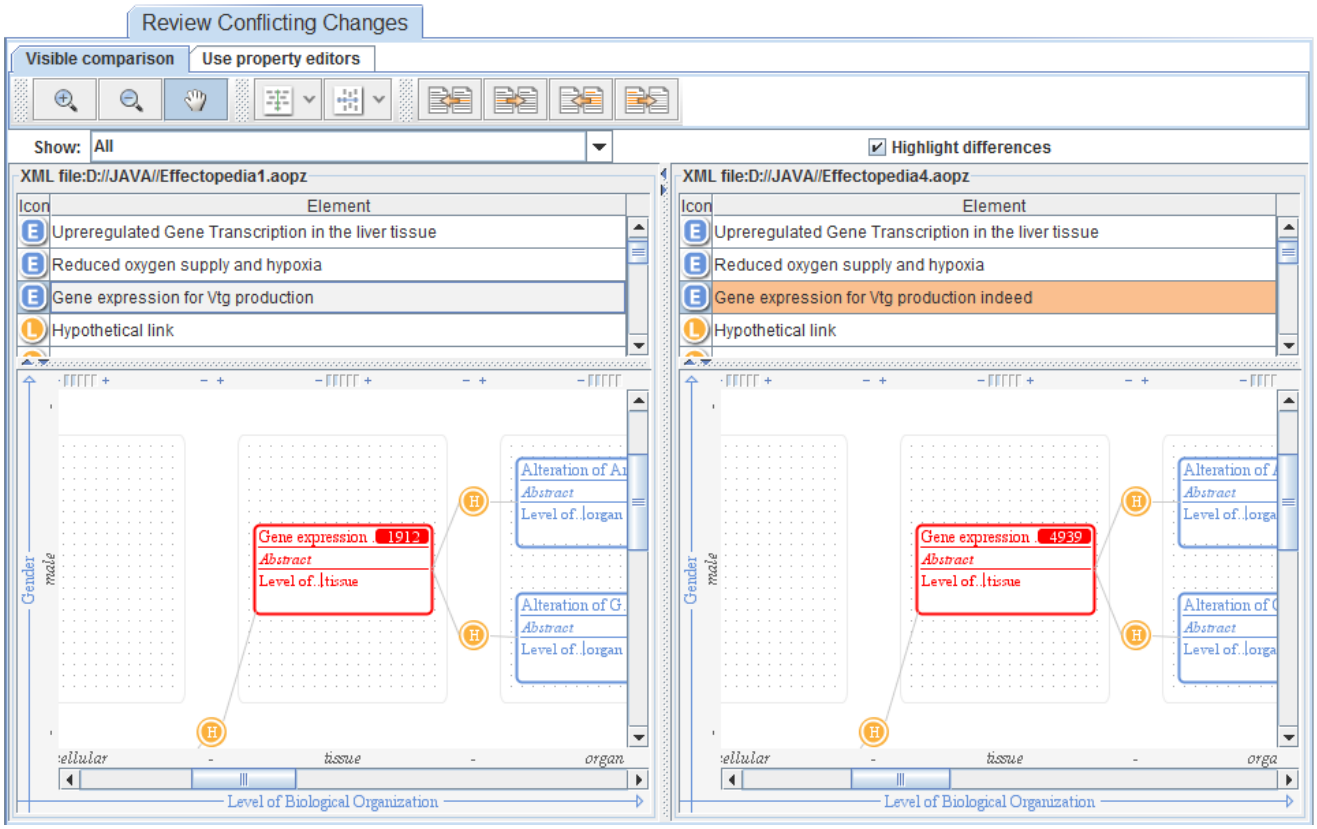
In the current version you can add new plain text reference element by pressing add ⊞ button. You can remove the selected reference entry by pressing ⊟ , and remove all entries by pressing on the reset ⊠ button. You can use the discuss button ⊡ to start a discussion on the relevance and significance of particular reference for the edited component or in future versions of Effectopedia sing in and initiate a chat on that subject.

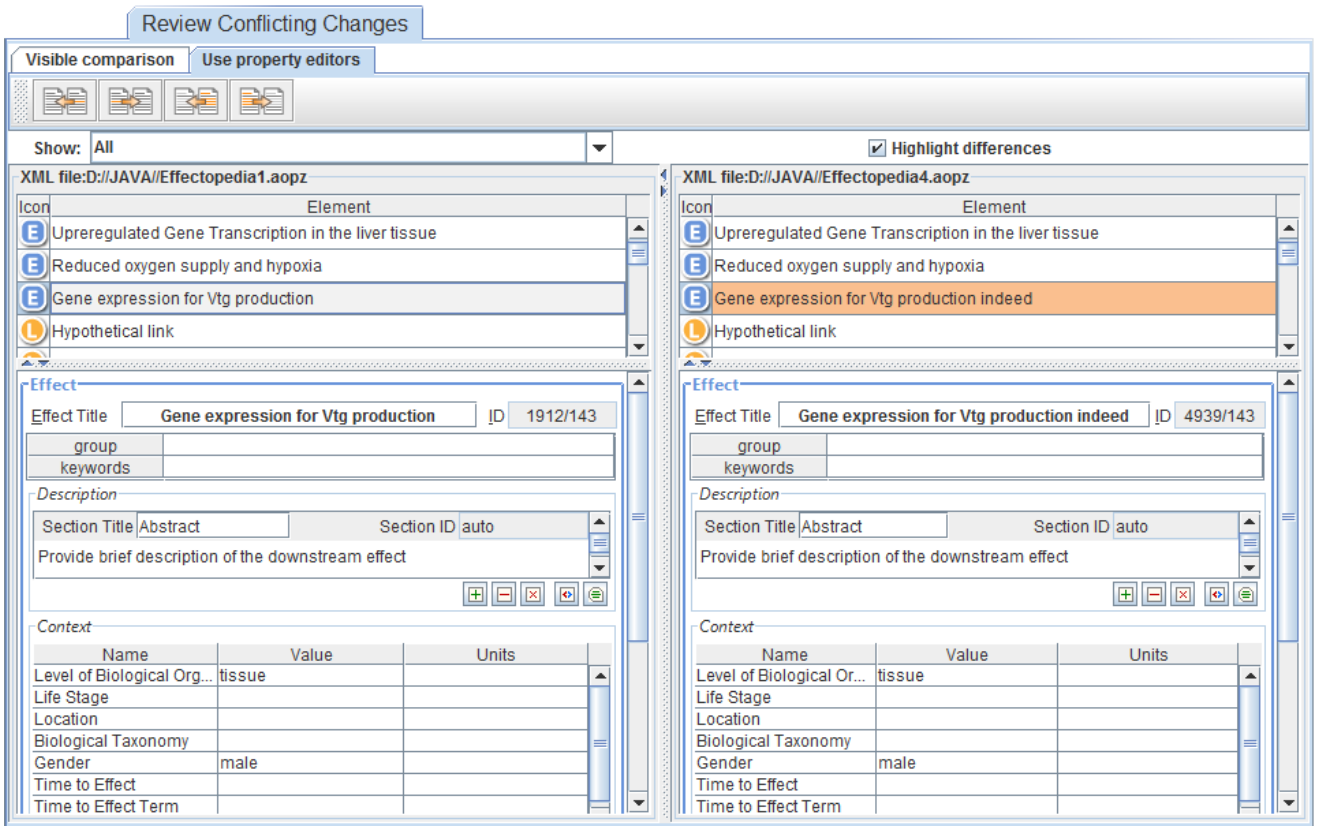


Manage Conflicting Changes

Conflicting changes occur when two users of Effectopedia make parallel edits of one and the same pathway element. As a result conflict occurs when trying to write back to the repository both versions. Such conflicts are presented to the user to resolve. Specially build interface for that will be loaded in detecting of such conflicts.

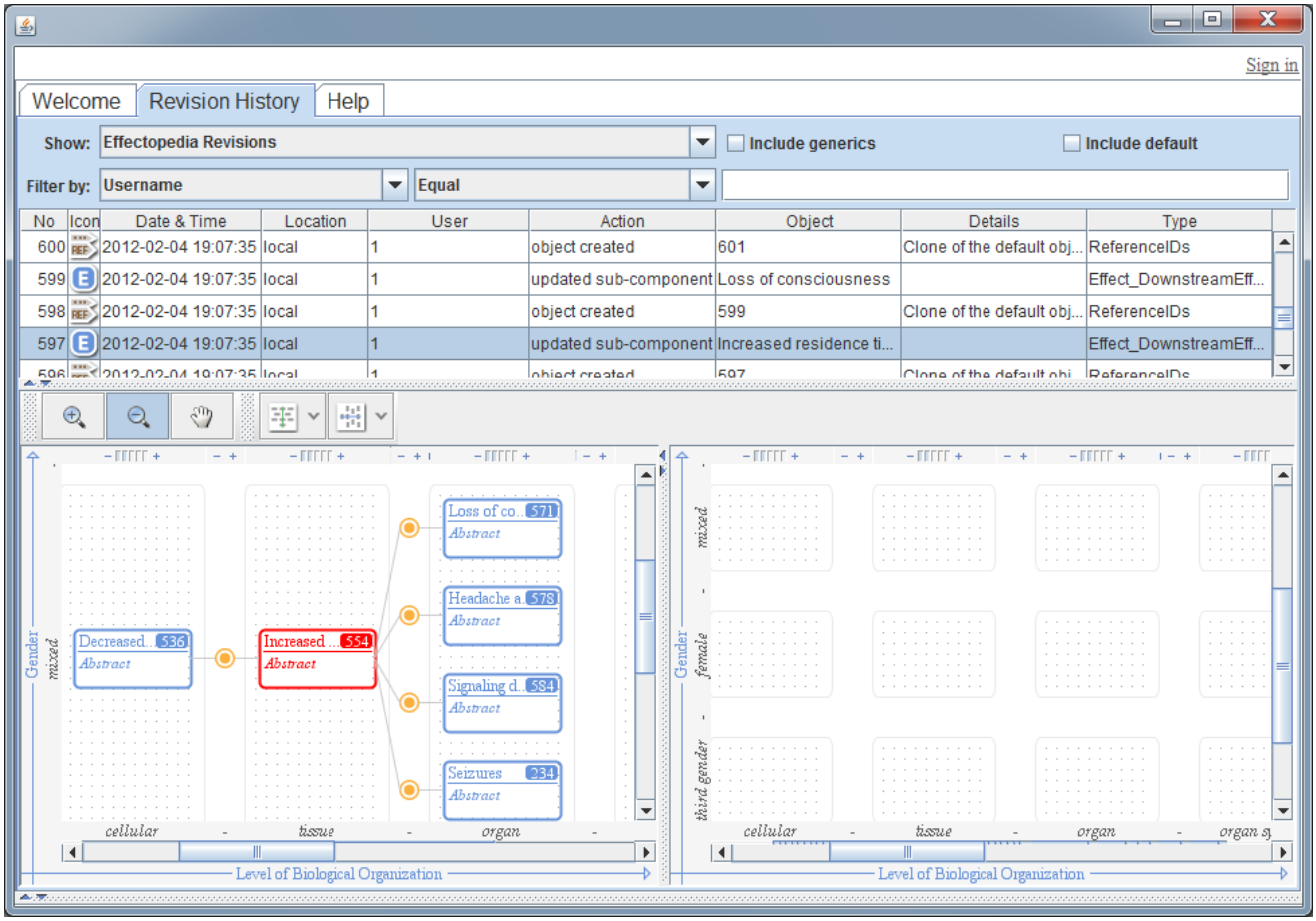
The interface is split in two major parts. Upper part contains some control functions and actions along with a customizable list of changes. The bottom part can contain visual information or dedicated editors (depending on the active tab on the very top of the conflict resolving interface)




Review Conflicting Changes
Visible comparison
Use property editors
Show: All
Highlight differences
XML file:D://JAVA//Effectopedia1.aopz
Icon
Element
Upreregulated Gene Transcription in the liver tissue
Reduced oxygen supply and hypoxia
Gene expression for Vtg production
Hypothetical link
Effect
Effect Title
Gene expression for Vtg production
ID
1912/143
group
keywords
Description
Section Title
Abstract
Section ID
auto
Provide brief description of the downstream effect
Context
Name
Value
Units
Level of Biological Org...
tissue
Life Stage
Location
Biological Taxonomy
Gender
male
Time to Effect
Time to Effect Term
XML file:D://JAVA//Effectopedia4.aopz
Icon
Element
Upreregulated Gene Transcription in the liver tissue
Reduced oxygen supply and hypoxia
Gene expression for Vtg production indeed
Hypothetical link
Effect
Effect Title
Gene expression for Vtg production indeed
ID
4939/143
group
keywords
Description
Section Title
Abstract
Section ID
auto
Provide brief description of the downstream effect
Context
Name
Value
Units
Level of Biological Or...
tissue
Life Stage
Location
Biological Taxonomy
Gender
male
Time to Effect
Time to Effect Term

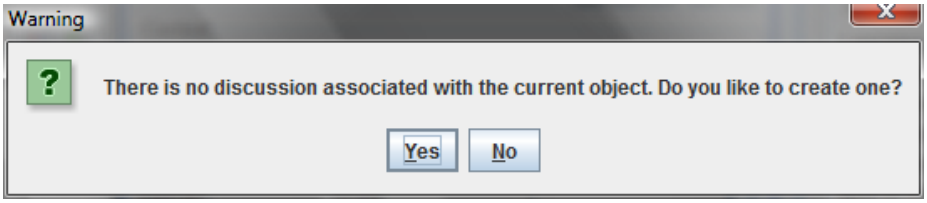
Review revision history

Effectopedia Revision history in currently in pre-alpha stages of development and is provided as a glimpse into an important future feature of Effectopedia application. The goal of revision history is to provide tools for visual exploration and comparison of the current version of the Effectopedia knowledge with previous (historical) revisions. The interface will also serve as more detailed undo / redo history for both the local current session and general edits by various users of the selected data source. Currently the interface shows a flat view to actions performed by the users. These actions could be filtered by their type or contributing user. The list of actions could be also sorted by clicking on the title of the column which is going to be used as a index.



Creating a new Discussion Topic

Creation of discussion topic can be done from multiple locations in the interface where discussion button is available. When you click on the discussion button the system checks if there is any discussion associated with the current object. If there is the discussion interface shows loaded with the topic. If there no discussion is associated with the current object and you are signed in the following dialog appears:



In order to create new discussion topics or posts you need to be signed in. In case you are not signed in the message dialog above asks you to sign in before you can create the new discussion topic.

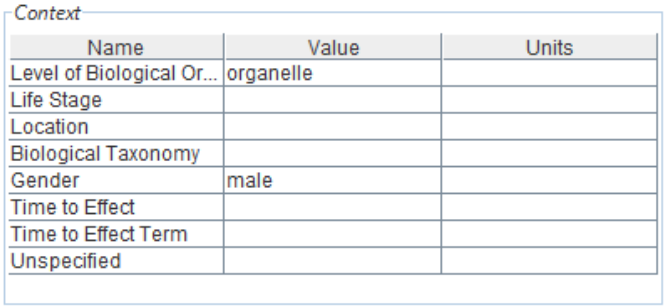
Working with the discussion interface

Appendix

1. Context editor

Context editor

The context editor allows editing the values the context dimensions of the current element. It is important to fill as many dimensions as possible and make them as inclusive as possible.



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