

OpenTox Services and Applications

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Berlin, Germany
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Introduction

OpenTox has developed a novel semantic interoperable computing architecture for the field of predictive toxicology.

Today I will review what OpenTox services and applications can do.

OpenTox is an Integrating Framework

Framework

- Toxicity Data (Linked)
- *in silico* models
- Validation & Reporting
- Interpretation aids

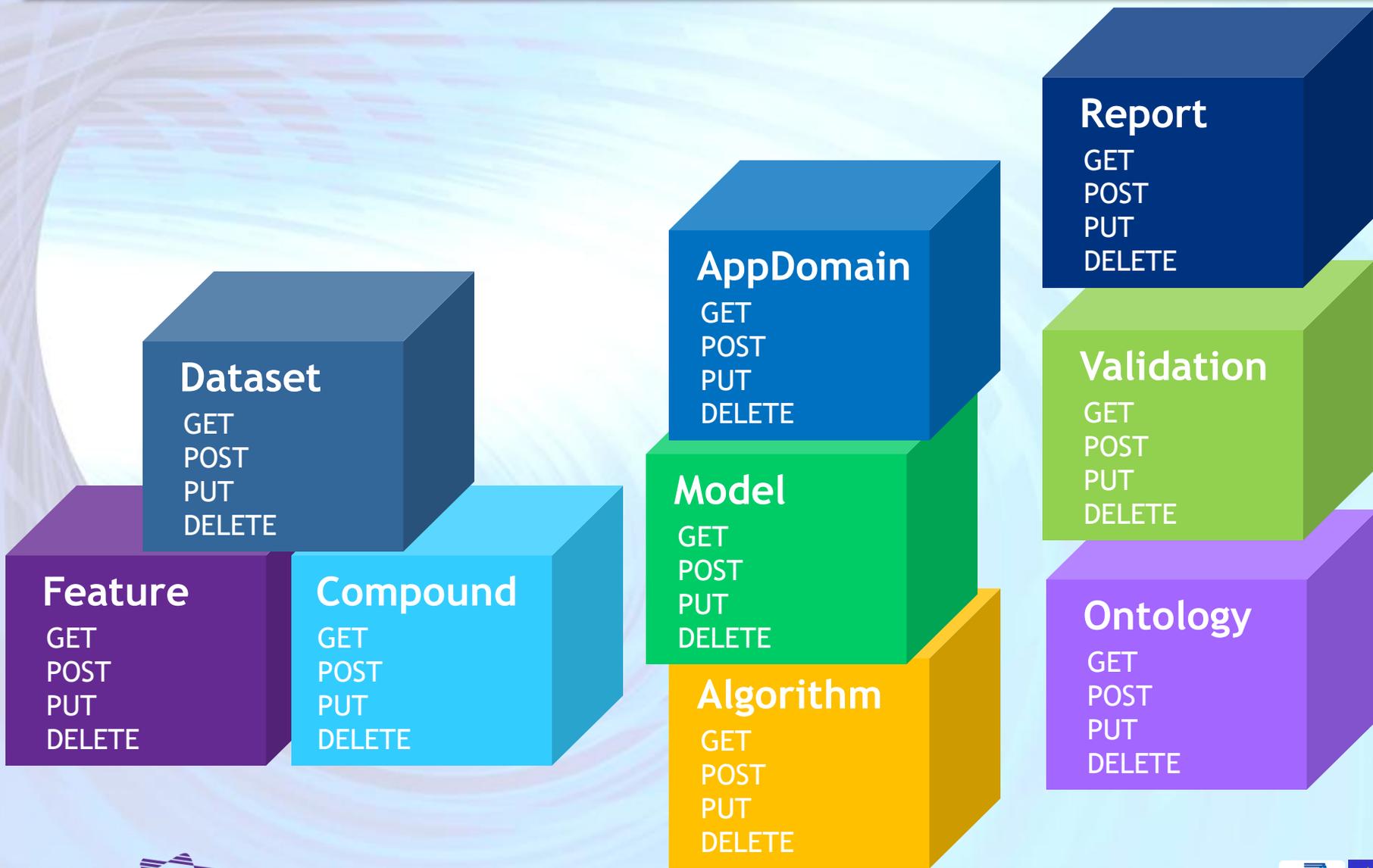
Diverse Access

- Toxicologist, Biologist, Chemists
- Computational Scientists
- Interfaces for new algorithm development & integration

Interoperability

- Promote Standards
- Core Open Source Components
- Support Ontologies & Integration of Multiple Resources

Overview of OpenTox Application Programming Interfaces



The OpenTox Framework (reported last year)

Collaborative development of predictive toxicology applications

Journal of Cheminformatics 2010, 2:7 doi:10.1186/1758-2946-2-7

Barry Hardy, Nicki Douglas, Christoph Helma, Micha Rautenberg, Nina Jeliaskova, Vedrin Jeliaskov, Ivelina Nikolova, Romualdo Benigni, Olga Tcheremenskaia, Stefan Kramer, Tobias Girschick, Fabian Buchwald, Joerg Wicker, Andreas Karwath, Martin Gutlein, Andreas Maunz, Haralambos Sarimveis, Georgia Melagraki, Antreas Afantitis, Pantelis Sopasakis, David Gallagher, Vladimir Poroikov, Dmitry Filimonov, Alexey Zakharov, Alexey Lagunin, Tatyana Glorizova, Sergey Novikov, Natalia Skvortsova, Dmitry Druzhilovsky, Sunil Chawla, Indira Ghosh, Surajit Ray, Hitesh Patel and Sylvia Escher

Open Access publication available at
www.jcheminf.com/content/2/1/7

What you can do with it ...

Endpoint	Model	Descriptors	Training dataset	Algorithm
	<input checked="" type="checkbox"/> OpenTox model created with TUM's kNNregression model learning web service.	YES	http://opentox.informatik.tu-muenchen.de:8080/OpenTox-dev/algorithm/kNNregression	
Carcinogenicity	<input checked="" type="checkbox"/> ToxTree: Benigni/Bossa rules for carcinogenicity and mutagenicity	-		ToxTree: Benigni/Bossa rules for carcinogenicity and mutagenicity
Dissociation constant (pKa)	<input checked="" type="checkbox"/> pKa	-		pKa
Endpoints	<input checked="" type="checkbox"/> ToxTree: Structure Alerts for the in vivo micronucleus assay in rodents	-		ToxTree: Structure Alerts for the in vivo micronucleus assay in rodents
Endpoints	<input checked="" type="checkbox"/> ToxTree: Michael acceptors	-		ToxTree: Michael acceptors
Eye irritation/corrosion	<input checked="" type="checkbox"/> ToxTree: Eye irritation	-		ToxTree: Eye irritation
Human health effects	<input checked="" type="checkbox"/> ToxTree: Extended Cramer rules	-		ToxTree: Extended Cramer rules
Human health effects	<input checked="" type="checkbox"/> ToxTree: ILSI/Kroes decision tree for TTC	-		ToxTree: ILSI/Kroes decision tree for TTC
Skin irritation/corrosion	<input checked="" type="checkbox"/> ToxTree: Skin irritation	-		ToxTree: Skin irritation

Simple building of predictive toxicology applications based on well-established methods and databases

What you can do with it ...

The image displays two overlapping windows. The top window is a Mozilla Firefox browser showing the ToxPredict application. The URL is <http://apps.ideaconsult.net:8180/ToxPredict/user/4996263b-9d7c-4fec-8b68-15e38c29e7cd/A/step3>. The page title is "ToxPredict OpenTox demo application". It features two main steps: "Step 1: Search Select structure(s)" and "Step 2: Verify structure Verify structure". Below these steps is a table listing various endpoints and their corresponding models.

Endpoint	Model
	OpenTox model created by TUM's kNN regression machine learning web service.
Carcinogenicity	ToxTree: Benigni/Boss for carcinogenicity and mutagenicity
Dissociation constant (pKa)	pKa
Endpoints	ToxTree: Structure Alerts for the in vivo micronucleus test in rodents
Endpoints	ToxTree: Michael acceptance rules
Eye irritation/corrosion	ToxTree: Eye irritation/corrosion
Human health effects	ToxTree: Extended Cr rules
Human health effects	ToxTree: ILSI/Kroes criteria tree for TTC
Skin irritation/corrosion	ToxTree: Skin irritation/corrosion

The bottom window is Taverna Workbench 2.1.0, showing a workflow diagram. The diagram consists of several interconnected tasks: "ask_username", "ask_password", "choose_trainset", "upload_trainset", "wait_for_trainset", "calculate_descriptors", "choose_prediction_feature", "learn_model", "wait_for_learned_model", "dataset_service_value_1", "apply_model_to_testset", "wait_for_prediction", and "result". The workflow starts with user authentication, followed by dataset selection and processing, model training, and finally applying the model to a test set to produce a result.

Simple building blocks for applications

Distributed applications with a wide range of methods and algorithms

Integration into workflow systems for computational biology

Need for Applications for REACH



REACH and (Q)SAR bottlenecks

Wim De Coen, ECHA, “*Current Challenges from Evaluation Point of View - Introduction Case Studies*”, ECHA Experts Workshop on “Dealing with Uncertainty of Non-Test Methods under REACH”, 2010:

Specific Bottlenecks for (Q)SAR:

- Well standardized and accepted OECD principles
- Issues mainly at level of documentation
 - Level of documentation insufficient
 - QMRF, QPRF missing
 - Applicability domain unclear
 - Unclear training datasets & algorithm
 - General issue of well established/commercial QSAR packages

REACH and data bottlenecks

There exists considerable uncertainty in decision making based on current reproductive toxicity data, which place the largest potential demands on animal testing required by REACH.

Improvements to reduce uncertainty in decision making require:
a “robust reference dataset of harmonised test information”

Reference: Dick Sijm and Betty Hakkert, RIVM, *“Use of non-test methods in integrated testing strategies for making informed decisions - Non-test methods require robust reference datasets”*, ECHA Experts Workshop on “Dealing with Uncertainty of Non-Test Methods under REACH”, 2010)

(Q)SARs & REACH requirements

(Quantitative) Structure Activity Relationship = (Q)SAR

According to REACH Annex XI, (Q)SAR results may be used instead of testing when all of the following conditions are met:

- The results are derived from a (Q)SAR model whose **scientific validity** has been established.
- The substance falls within the **applicability domain** of the (Q)SAR model.
- The results are **adequate** for the purpose of classification and labeling and/or risk assessment.
- Adequate and reliable **documentation** of the applied method is provided.

ToxCreate - (Q)SAR Model Building application

The screenshot shows a web browser window titled "ToxCreate - Mozilla Firefox" with the address bar displaying "http://www.toxcreate.org/create". The page content includes a navigation menu with "Create", "Inspect", "Predict", "Login", and "Help". A blue box contains the text "This service creates" followed by a bulleted list: "• *lazar classification* models and" and "• *lazar regression* models". Below this, it says "from your uploaded datasets. Further modelling algorithms will be added in future versions. Please read the [instructions for creating training datasets](#) before submitting." A form area prompts the user to "Select training data in [Excel](#) or [CSV](#) format:" and shows a file input field with the path "e:\vergleich\tmp\hamster_carcinogenicity.csv" and a "Durchsuchen..." button. Below the input field are "Create model" and "Cancel" buttons. The user is identified as "User: guest". A footer note states: "You are currently logged in as **guest** and your models can be modified or deleted by other guests. Please [log in](#) with your **OpenTox** account to control your model permissions."

Create and evaluate models to predict toxicity

ToxCreate

Create Inspect Predict Login Help

User: **guest**

This service creates

- *lazar classification* models and
- *lazar regression* models

from your uploaded datasets. Further modelling algorithms will be added in future versions. Please read the [instructions for creating training datasets](#) before submitting.

Select training data in [Excel](#) or [CSV](#) format:

e:\vergleich\tmp\hamster_carcinogenicity.csv

[Cancel](#)

You are currently logged in as **guest** and your models can be modified or deleted by other guests. Please [log in](#) with your **OpenTox** account to control your model permissions.

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Developed by In Silico Toxicology

ToxCreate - (Q)SAR Model Results

ToxCreate - Mozilla Firefox
Datei Bearbeiten Ansicht Chronik Lesezeichen Extras Hilfe
TC http://www.toxcreate.org/models
TC ToxCreate

Create and evaluate models to predict toxicity **ToxCreate**

Create Inspect Predict Login Help

User: **guest**

Get an overview about ToxCreate models. Parts of this page are refreshed every 5 seconds to update the model status.

Hamster Carcinogenicity (edit)

Status: Completed(delete)
Training compounds: 85
Algorithm: lazar
Type: classification
Descriptors: Fminer backbone refinement classes
Training dataset: Excel sheet , YAML (experts)
Feature dataset: Excel sheet , YAML (experts)
Model: QMRF Editor, YAML (experts, models cannot be represented in Excel)

Validation:
Detailed report: show
Number of predictions: 69
Correct predictions: 82.68 %
Weighted area under ROC: 0.935
Specificity: 0.143
Sensitivity: 0.865

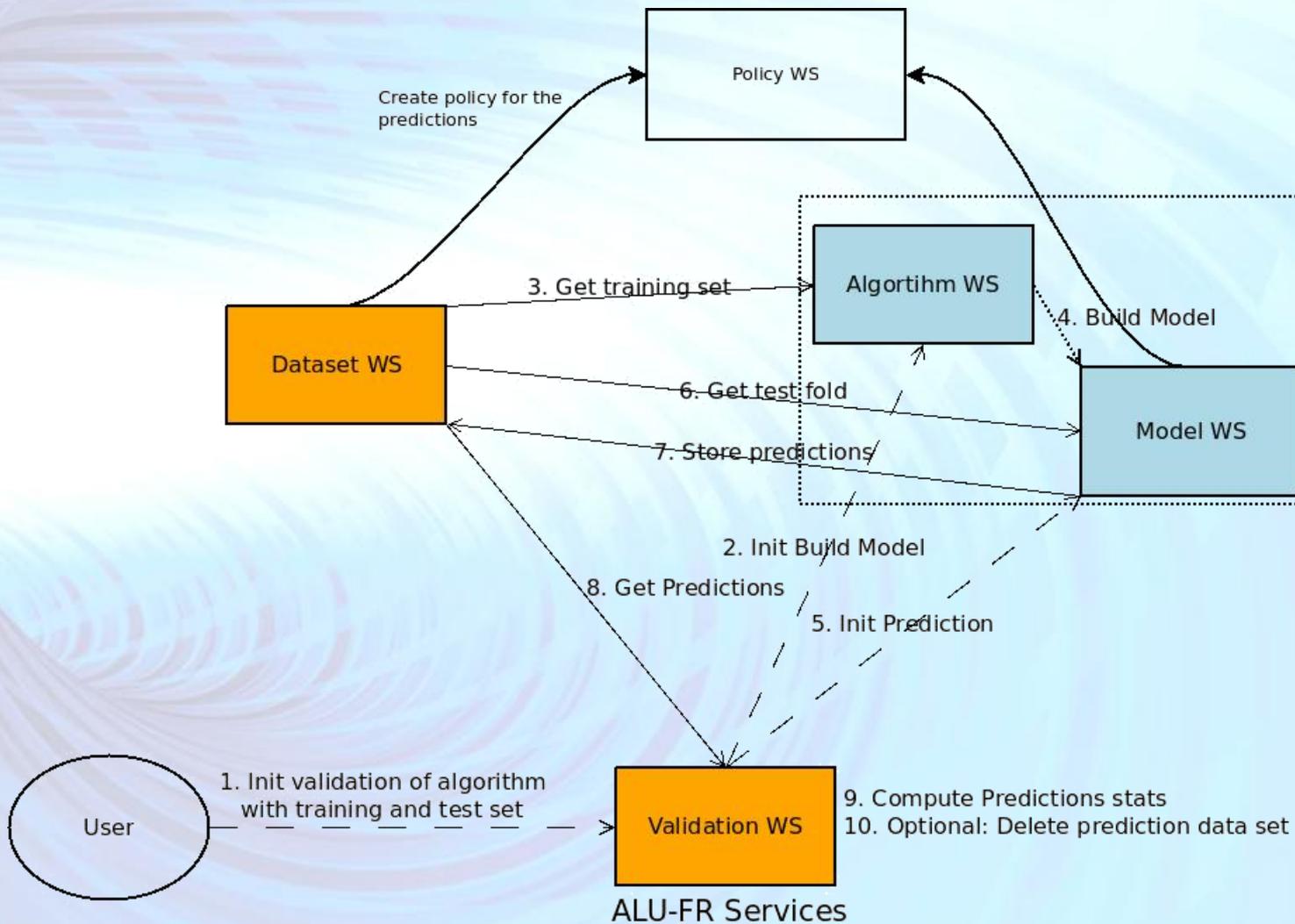
Confusion Matrix:

		Measured	
		active	inactive
Predicted	active	32	5
	inactive	7	25

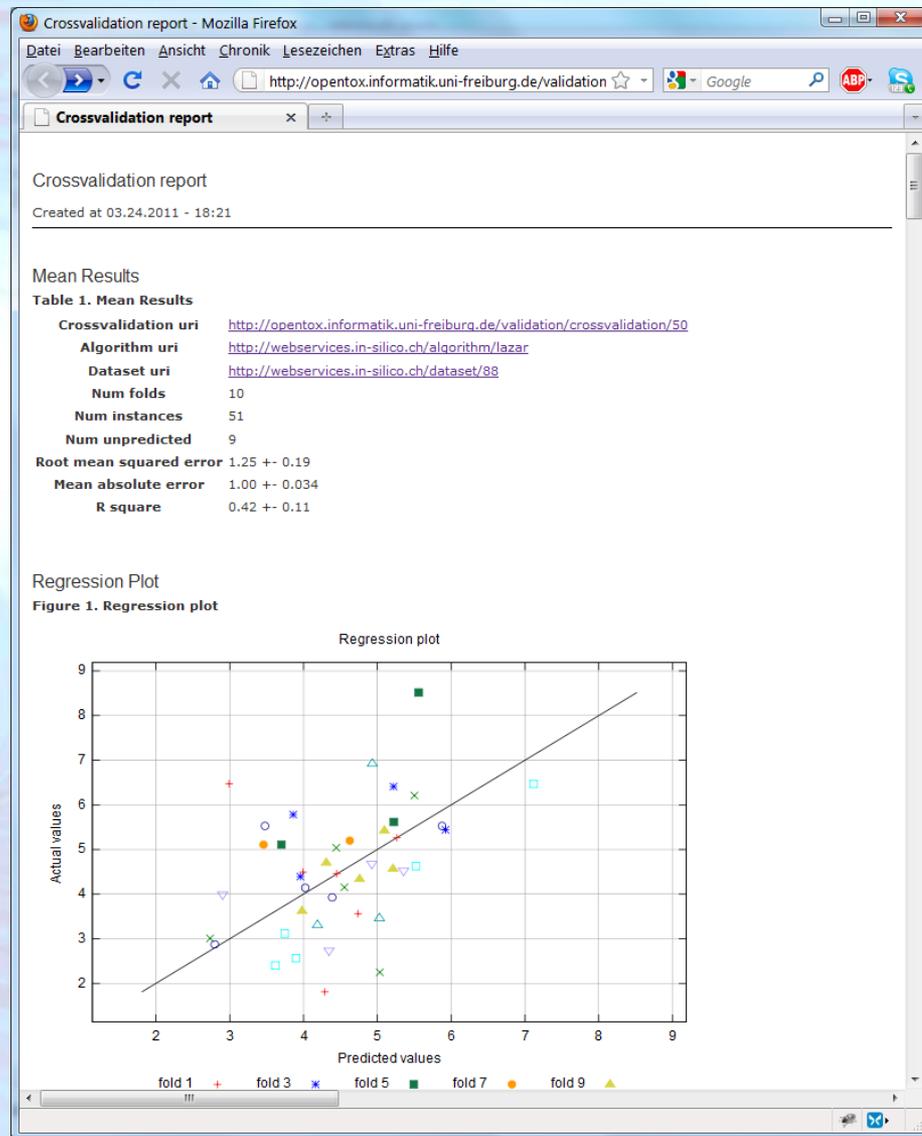
© in silico toxicology 2009-2010, powered by OpenTox

	OECD Principle	OpenTox addresses Validation Principles by...
1	Defined Endpoint	providing a unified source of well defined and documented toxicity data with a common vocabulary
2	Unambiguous Algorithm	providing transparent access to well documented models and algorithms as well as to the source code
3	Defined Applicability Domain	integrating tools for the determination of applicability domains during the validation of prediction models
4	Goodness-of-fit, robustness and predictivity	providing scientifically sound validation routines for the determination of errors and confidences
5	Mechanistic interpretation (if possible)	integrating tools for the inference, correlation or prediction of toxicological mechanisms and the recording of opinions and analysis in reports

Validation within OpenTox



ToxCreate - linked to Validation Service



ToxCreate - Confidence, Supporting Information

TC ToxCreate

phenylhydrazine (CHEBI:27924)

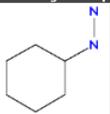
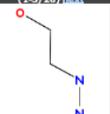
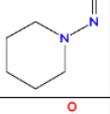
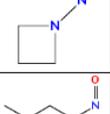
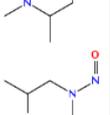
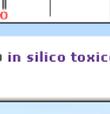
Create and evaluate models to predict toxicity

ToxCreate

Create Inspect **Predict** Login Help

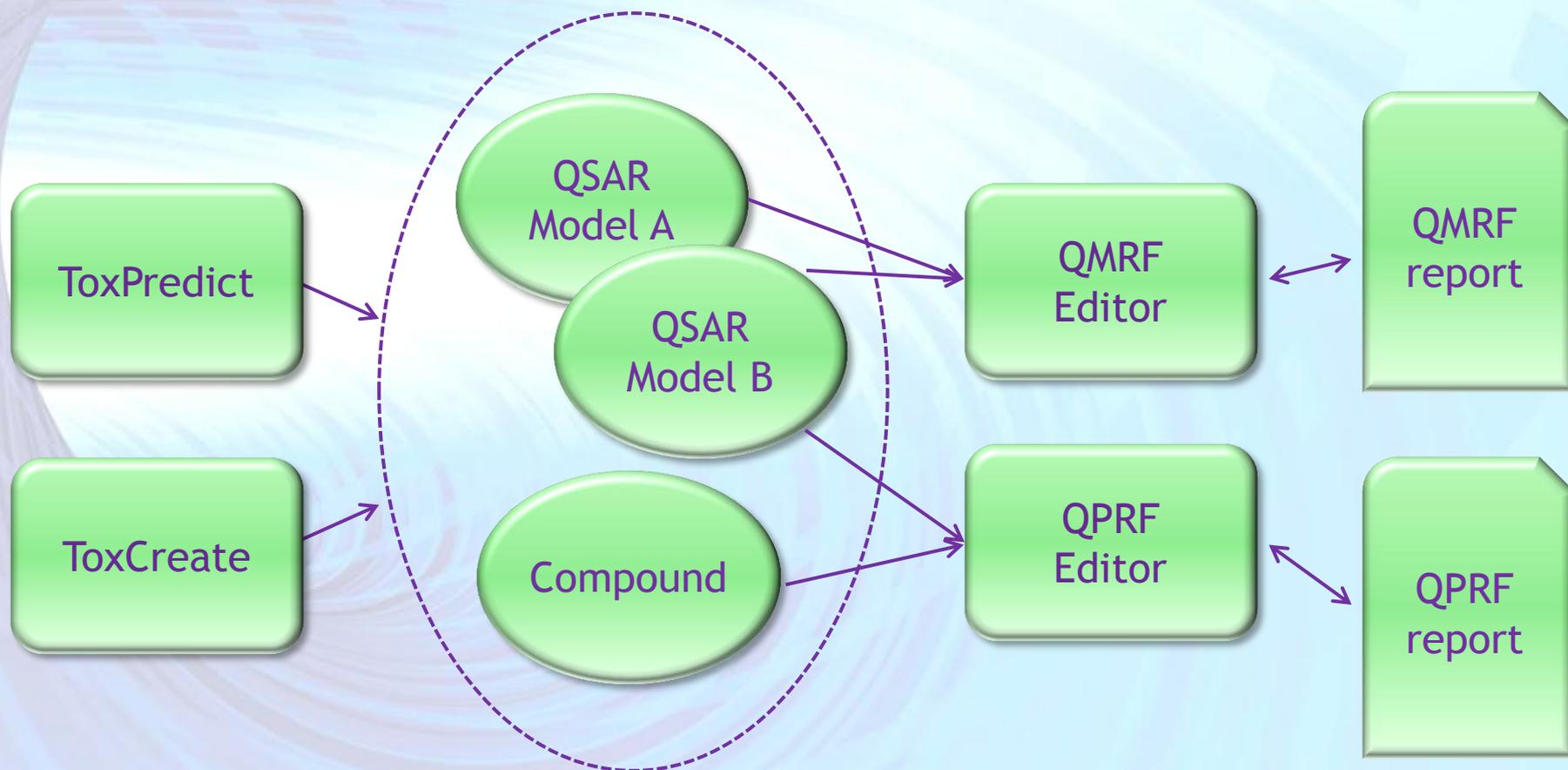
User: **guest**

New prediction

Hamster Carcinogenicity	Prediction	Confidence	Supporting information
 active		0.108	Names and synonyms Significant fragments
Neighbors (1-5726) next	Measured activity	Similarity	Supporting information
 inactive		0.715	Names and synonyms Significant fragments
 inactive		0.5	Names and synonyms Significant fragments
 inactive		0.5	Names and synonyms Significant fragments
 inactive		0.5	Names and synonyms Significant fragments
 inactive		0.5	Names and synonyms Significant fragments

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(Q)SARs - reporting in OpenTox



(Q)SARs - QMRF reporting in OpenTox

QMRF Editor 0.05 OpenTox Version http://opentox.informatik.uni-freiburg.de/validation/reach_report/QMRF/3

File Edit Style

QMRF (Q)SAR Model Reporting Format (QMRF), Version 1.2

Welcome Version

Name

Section 1. Author

Section 2. Date

Section 3. Contact

Section 4. Email

www

Section 5.

Section 6.

Background

Section 7. The set of information that you provide will be used for the validation of (Q)SARs. For this purpose, the structure of the QMRF is devised to reflect as much as possible the OECD principles for the validation, for regulatory purposes, of (Q)SAR models.

Section 8. You are invited to consult the OECD "Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship Models" that can aid you in filling in a number of fields of the QMRF (visit the following webpage for downloading the proper documentation: http://ecb.jrc.it/qsar/background/background_oecd_principles.php)

Section 9.

Section 10.

Submission Procedure

If you wish to submit the QMRF for inclusion in the JRC QSAR Model Database, please save your QMRF as xml file and upload it by the on-line submission procedure

Download started in progress

Eingabe

?

Please enter the URI for the download

OK Abbrechen

QPRF Reporting (Qedit)

The screenshot displays the Qedit software interface. The main window is titled "/home/chung/Desktop/phenobarn" and has tabs for "1. Substance", "2. General Information", "3. Prediction", and "4. Adequacy Info". The "3. Prediction" tab is active, showing sub-sections for "Model", "Prediction", and "Applicability Domain".

3.3. Applicability Domain Info.

Name Applicability Domain Estimation Algorithm Used :

Link to Applicability Domain Resource :

3.3.b. Structural Analogues

Add Compound Wizard Remove Clear List Similarity Level: Acquire List of Analogues Compound Info

List of Structural Analogues (URIs):

Chemical Name	Experimental Value
phenobarbital, Phen...	
5-methyl-5-phenylb...	
methylphenobarbit...	
5-allyl-5-phenylbarbi...	
primidone, Primacl...	
calcium bis[5-(1-cyc...	
5-ethyl-5-(4'-hydrox...	
barbexaclone	
1,3-dimethyl-5-phen...	
5-ethyl-5-phenylbar...	
N-(acetaminophen)	

Image of structural analogue:

3.3.c. Consideration

Discussion

Applicability Domain Result: ✔

3.3.a. Choose Domain :

Compound Details

URI:

Smiles:

InChI:

InChI Key:

CAS number:

Chemical Name:

Einecs:

REACH Reg. Date:

Available Conformers (Links):

-
-
-

Buttons:

Application by Pantelis Sopsakis (NTUA)

Metabolites

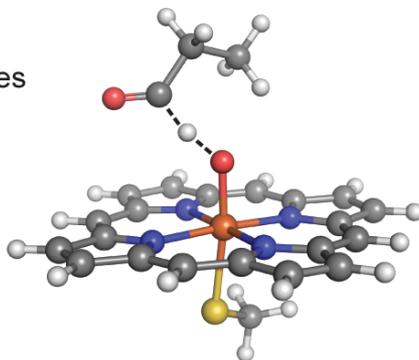
According to ECHA Guidance B, further investigation may be required for degradation products and metabolites if considered relevant for the chemical safety assessment, PBT assessment or classification and labeling.

SMARTCyp Service for Predicting Metabolites

Atom Reactivity Library

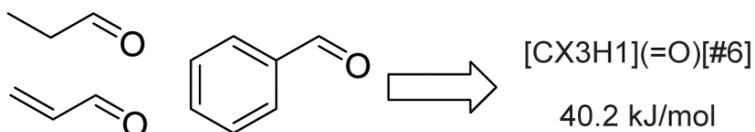
A. Calculate Quantum Chemical Reference Energies

Calculate transition state energies using density functional theory



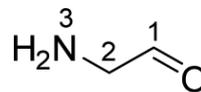
B. Define SMARTS Rules

Group calculations by fragments and calculate average energies



SMARTCyp

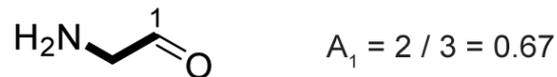
1. Assign Energies By SMARTS matching



Atom	SMARTS	Energy
1	<chem>[CX3H1](=O)[#6]</chem>	40.2
2	<chem>[CX4][N]</chem>	39.8
3	<chem>[N^3][H1,H2]</chem>	54.1

2. Compute Accessibility Descriptor

$$A_i = \text{Maxbonds}_i / \text{Maxbonds}_{\text{all}}$$



3. Compute Score and Rank Atoms

Score, $S = E - 8A$
Lowest score gets rank 1

$$S_1 = 40.2 - 8 \cdot 0.67 = 34.84$$

$$S_2 = 39.8 - 8 \cdot 0.67 = 34.44$$

$$S_3 = 54.1 - 8 \cdot 1.00 = 46.10$$

Atom 1 - Rank 2

Atom 2 - Rank 1

Atom 3 - Rank 3

SMARTCyp - developed by Patrik Rydberg, University of Copenhagen

www.farma.ku.dk/index.php/SMARTCyp/7990/0/

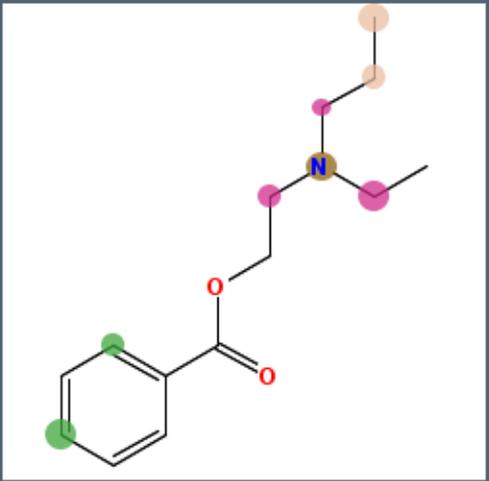
Metabolites

[ToxPredict](#) [TTC Depiction](#) [Datasets](#) [Chemical compounds](#) [Similarity](#) [Substructure](#) [playground](#) [Help](#)



Search by property or identifier name (optional) and value

This site and AMBIT REST services are under development!



-  Aliphatic Hydroxylation
-  Aromatic Hydroxylation
-  N-Dealkylation
-  N-Oxidation
-  O-Dealkylation
-  S-Oxidation

Developed by Ideaconsult

Information Gathering & Evaluation Process

Annex VI of REACH describes four steps of the Information Gathering and Evaluation Process (IGEP) that need to be followed by the registrant to fulfill the information requirements for a substance:

Step 1 Gather and share existing information

Step 2 Consider information needs

Step 3 Identify information gaps

Step 4 Generate new information or propose a testing strategy

Information Gathering & Evaluation Process

In step 1 of the IGEP, the registrant must collect all existing *in vivo* toxicological and ecotoxicological information that is relevant and available to him regardless of whether information on a given endpoint is required or not at the specific tonnage level.

The Part B guidance states that this information may be obtained from a variety of sources including “databases or other sources in the open literature or accessible on the internet”.

Step 1: Search
Select structure(s)

Step 2: Verify structure
Verify structure

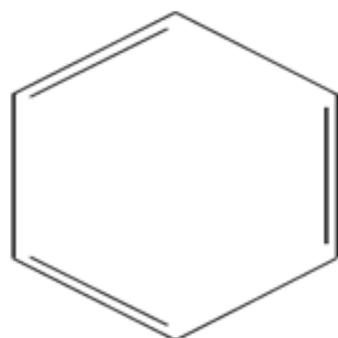
Step 3: Models
Select prediction models

Step 4: Estimate
Estimate

Step 5: Results
Display results

This page lists your ToxPredict workflow results for the structure(s) you have selected and the model prediction(s) you have chosen to run. You could also retrieve the ToxPredict report in various other formats, e.g. [SDF](#), [CML](#), [SMI](#), [PDF](#), [CSV](#), [ARFF](#), [RDF/XML](#) or [RDF/N3](#).

Download as 



CAS RN
EINECS
IUPAC name
Synonym

71-43-2
200-753-7
benzene
(6)annulene; benzine; Benzol; Benzolene;
bicarburet of hydrogen; carbon oil; Coal naphtha;
cyclohexatriene; mineral naphtha; motor benzol;
nitration benzene; Phene; Phenyl hydride;
pyrobenzol.

Synonym
Synonym
Synonym
Quality label

21742.0
Benzene
benzene
OK

MolecularWeight  **MolecularWeight**

MW

78.1112

Information Gathering & Evaluation Process

Select

ToxPredict
OpenTox demo application

Welcome, [guest](#)
[Admin](#)
[Help](#)

1. Select structure(s) → 2. Verify structure(s) → 3. Select model(s) → 4. Run prediction(s) → 5. Display result(s) → **NEXT**

Model	Endpoint	Algorithm	Validation
<input checked="" type="checkbox"/> MolecularWeight		MolecularWeight	
<input checked="" type="checkbox"/> ToxTree: Verhaar scheme for predicting toxicity mode of action	Acute toxicity to fish (lethality)	ToxTree: Verhaar scheme for predicting toxicity mode of action	
<input checked="" type="checkbox"/> ToxTree: Benigni/Bossa rules for carcinogenicity and mutagenicity	Carcinogenicity	ToxTree: Benigni/Bossa rules for carcinogenicity and mutagenicity	
<input checked="" type="checkbox"/> pKa	Dissociation constant (pKa)	pKa	
<input checked="" type="checkbox"/> ToxTree: Structure Alerts for the in vivo micronucleus assay in rodents	Endpoints	ToxTree: Structure Alerts for the in vivo micronucleus assay in rodents	
<input checked="" type="checkbox"/> ToxTree: Michael acceptors	Endpoints	ToxTree: Michael acceptors	
<input checked="" type="checkbox"/> ToxTree: Eye irritation	Eye irritation/corrosion	ToxTree: Eye irritation	
<input checked="" type="checkbox"/> Caco-2 Cell Permeability http://www.ncbi.nlm.nih.gov/pubmed/16959190	Gastrointestinal absorption	Regression: Linear regression	Model validation report
<input checked="" type="checkbox"/> OpenTox model created with TUM's PL SRegression model learning web service.	Gastrointestinal absorption	http://opentox.informatik.tu-muenchen.de:8080/OpenTox-dev/algorithm/PLSRegression	
<input checked="" type="checkbox"/> OpenTox model created with TUM's kNNregression model learning web service.	Gastrointestinal absorption	http://opentox.informatik.tu-muenchen.de:8080/OpenTox-dev/algorithm/kNNregression	
<input checked="" type="checkbox"/> http://opentox.ntua.gr:3000/model/679a80e6-b2d9-45c1-ba42-4489e85b5898	Gastrointestinal absorption	Multiple Linear Regression Training Algorithm	
<input checked="" type="checkbox"/> Lipinski Rule of Five	Human health effects	Lipinski Rule of Five	
<input checked="" type="checkbox"/> ToxTree: Cramer rules	Human health effects	ToxTree: Cramer rules	
<input checked="" type="checkbox"/> XLogP	Octanol-water partition coefficient (Kow)	XLogP	
<input checked="" type="checkbox"/> START biodegradation and persistence plug-in	Persistence: Biodegradation	START biodegradation and persistence plug-in	
<input checked="" type="checkbox"/> SmartCYP: Cytochrome P450-Mediated Drug Metabolism	Protein-binding	SmartCYP: Cytochrome P450-Mediated Drug Metabolism	
<input checked="" type="checkbox"/> ToxTree: Skin irritation	Skin irritation /corrosion	ToxTree: Skin irritation	
<input checked="" type="checkbox"/> ToxTree: Skin sensitisation alerts (M. Cronin)	Skin sensitisation	ToxTree: Skin sensitisation alerts (M. Cronin)	

Information Gathering & Evaluation Process

Display

ToxPredict

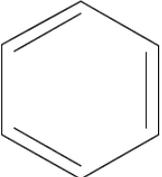
OpenTox demo application

Welcome [guest](#)
[Admin](#)
[Help](#)

1. Select structure(s) → 2. Verify structure(s) → 3. Select model(s) → 4. Run prediction(s) → 5. Display result(s)

<< Page 1 Records per page 1 >> [Structure\(s\) & Model predictions & Experimental Data](#) [SDF](#) [CSV](#) [PDF](#)

1.



CASRN 71-43-2

Synonym(s) benzene,(6)annulene; benzine; Benzol; Benzolene; bicarburet of hydrogen; carbon oil; Coal naphtha; cyclohexatriene; mineral naphtha; motor benzol; nitration benzene; Phene; Phenyl hydride; pyrobenzol, Benzene, BENZENE, C6H6

EINECS 200-753-7

IUPAC name benzene

InChIKey_std UHOVQNZJYSORNB-UHFFFAOYSA-N

InChI_std InChI=1S/C6H6/c1-2-4-6-5-3-1/h1-6H

REACHRegistrationDate 30.11.2010

SMILES c1ccccc1,C1=CC=CC=C1

benzene,(6)annulene; benzine; Benzol; Benzolene; bicarburet of hydrogen; carbon oil; Coal naphtha; cyclohexatriene; mineral naphtha; motor benzol; nitration benzene; Phene; Phenyl hydride; pyrobenzol, Benzene, BENZENE, C6H6

⚡ OpenTox model created with TUM's PLS regression model learning web service.

Prediction feature for http://apps.ideaconsult.net:8080/ambit2/feature/22200 endpoint prediction	-4.496099948883057
LipinskiFailures ⚡ Lipinski Rule of Five	
LipinskiFailures	0.0
Acute_toxicity_to_fish_lethality ⚡ ToxTree: Verhaar scheme for predicting toxicity mode of action Verhaar scheme	Class 1 (narcosis or baseline toxicity)
Carcinogenicity ⚡ ToxTree: Benigni/Bossa rules for carcinogenicity and mutagenicity	
Structural Alert for genotoxic carcinogenicity	NO
Structural Alert for nongenotoxic carcinogenicity	NO
Potential S. typhimurium TA100 mutagen based on QSAR	NO
Unlikely to be a S. typhimurium TA100 mutagen based on QSAR	NO
Potential carcinogen based on QSAR	NO
Unlikely to be a carcinogen based on QSAR	NO
For a better assessment a QSAR calculation could be applied.	NO
Negative for genotoxic carcinogenicity	YES
Negative for nongenotoxic carcinogenicity	YES
Structural Alert for genotoxic carcinogenicity#explanation	QSA1.Acyl halides No QSA2.Alkyl (C<5) or benzyl ester of sulphonic or phosphonic acid No QSA3.N-methylol derivatives No QSA4.Monohaloalkene No QSA5.S or N mustard No QSA6.Propiolactones and propiosultones No QSA7.Epoxides and aziridines No QSA8.Aliphatic halogens No

Done

Information Gathering & Evaluation Process

[ToxPredict](#) [TTC Depiction Datasets](#) [Chemical compounds](#) [Similarity](#) [Substructure](#) [Algorithms](#) [References](#) [Features](#) [Templates](#) [Models](#) [Ontology](#) [RDF playground](#) [Help](#)

ambit

This site and AMBIT REST services are under development!

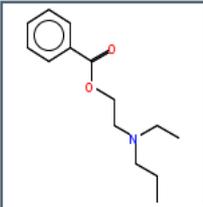
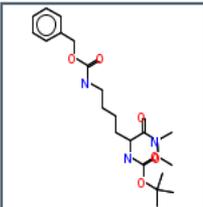
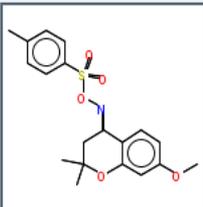
Features

Find	Name	Units	Same as	Origin (Dataset, Model or Algorithm)	Nominal values
	Structural Alert for genotoxic carcinogenicity		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Structural Alert for nongenotoxic carcinogenicity		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Potential <i>S. typhimurium</i> TA100 mutagen based on QSAR		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Unlikely to be a <i>S. typhimurium</i> TA100 mutagen based on QSAR		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Potential carcinogen based on QSAR		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Unlikely to be a carcinogen based on QSAR		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	For a better assessment a QSAR calculation could be applied.		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Negative for genotoxic carcinogenicity		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Negative for nongenotoxic carcinogenicity		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Error when applying the decision tree		http://www.opentox.org	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO

http://pirin.uni-plovdiv.bg:8080/malaria/feature/259

Information Gathering & Evaluation Process

Search results Property = Low (Class I) Download as  Max number of hits: 100

#	Compound	nature0910	nature0910	Benigni /	Benigni /
		Percentage inhibition 3D7	Percentage inhibition HEPG2	Structural Alert for genotoxic carcinogenicity	Structural Alert for nongenotoxic carcinogenicity
504		99.0	2.0	NO	NO
509		98.0	5.0	YES	NO
508		97.0	10.0	NO	NO
512		96.0	30.0	NO	NO

Done 

Information Requirements - *in vitro*

Two categories of *in vitro* methods are currently referred to within REACH as suitable:

- Validated methods. Examples include *in vitro* tests for skin corrosion and *in vitro* genotoxicity tests such as the Ames Salmonella typhimurium mutagenicity test.
- *In vitro* tests that meet internationally agreed pre-validation criteria from e.g. ECVAM.

A main criterion for acceptance for regulatory use is the adequacy of the information generated in such an *in vitro* assay for the purpose of classification and labeling and/or risk assessment.

ToxLink: ToxCast Ontology

Metadata(EPANCCTAssayOntology1.owl) OWLClasses Properties Individuals

SUBCLASS EXPLORER CLASS EDITOR for Assay (instance of owl:Class)

For Project: ●

For Class: <http://www.semanticweb.org/ontologies/2010/4/EPANCCTAssayOntology1.owl#Assay>

Property	
rdfs:comment	

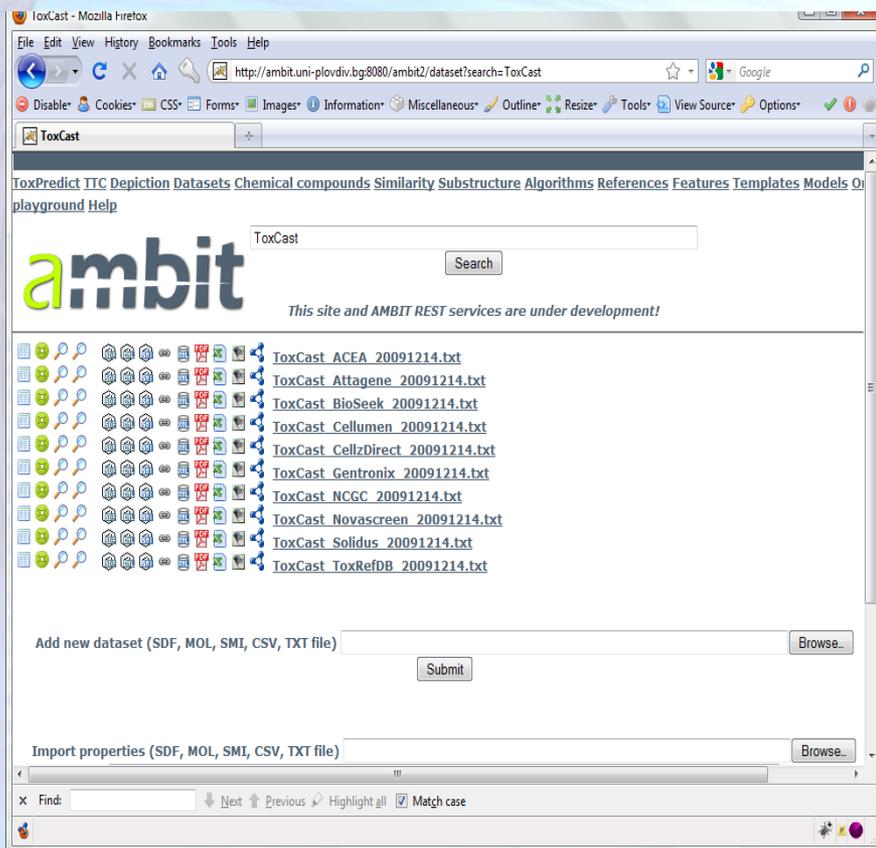
owl:Thing

www.opentox.org/dev/ontology/collaborative_protege

Example: ToxCast

Dataset service at
<http://ambit.uni-plovdiv.bg:8080/ambit2/dataset>

Query an OpenTox ontology service at
<http://ambit.uni-plovdiv.bg:8082/ontology>



```
PREFIX ot:<http://www.opentox.org/api/1.1#>
PREFIX ota:<http://www.opentox.org/algorithms.owl#>
PREFIX owl:<http://www.w3.org/2002/07/owl#>
PREFIX dc:<http://purl.org/dc/elements/1.1/>
PREFIX rdfs:<http://www.w3.org/2000/01/rdf-schema#>
PREFIX rdf:<http://www.w3.org/1999/02/22-rdf-syntax-ns#>
PREFIX otee:<http://www.opentox.org/echaEndpoints.owl#>
PREFIX toxcast:<http://www.opentox.org/toxcast#>

select *
where {
  ?Feature rdf:type ot:Feature.
  {?Feature dc:title ?title}.
  {?Feature owl:sameAs ?assay}.
  {?assay toxcast:gene ?geneid}.
  {?assay toxcast:hasProperty ?species}.
  {?species rdf:type toxcast:SPECIES}.
  {?assay toxcast:hasProperty ?target_source}.
  {?target_source rdf:type toxcast:ASSAY_TARGET_SOURCE}.
  {?assay toxcast:hasProperty ?target_family}.
  {?target_family rdf:type toxcast:ASSAY_TARGET_FAMILY}.
  {?assay toxcast:hasProperty ?target}.
  {?target rdf:type toxcast:ASSAY_TARGET}.
  {?assay toxcast:hasProperty toxcast:Cytochrome_P450}.
}

order by ?feature ?assay ?target
```

Example: ToxCast

```

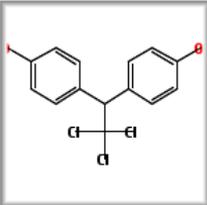
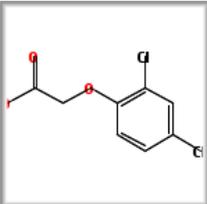
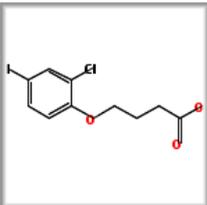
PREFIX ot:<http://www.opentox.org/
PREFIX ota:<http://www.opentox.org/
PREFIX owl:<http://www.w3.org/2002
PREFIX dc:<http://purl.org/dc/element
PREFIX rdfs:<http://www.w3.org/200
PREFIX rdf:<http://www.w3.org/1999
PREFIX otee:<http://www.opentox.org
PREFIX toxcast:<http://www.opentox.org

select ?Feature ?title ?id
where {
  ?Feature rdf:type ot:Feat
  {?Feature dc:title ?title}.
  {?Feature owl:sameAs ?assay}.
  {?assay toxcast:gene ?geneid}.
  {?assay toxcast:hasProperty ?genena
  {?genename rdf:type toxcast:GENE_
  }
  
```

Query an OpenTox ontology service
<http://ambit.uni-plovdiv.bg:8082>

Chemical compounds

Search results Dataset = 961 hits: 100

#	Compound	ToxCast At	Benigni /	Benigni /
		ATG RORE CIS	Structural Alert for genotoxic carcinogenicity	Structural Alert for nongenotoxic carcinogenicity
1		1000000.0	NO	NO
2		1000000.0	NO	NO
3		1000000.0	NO	NO
4		1000000.0	NO	NO

dataset/961?feat
 uni-
 feature/335126

Google

tox.org/toxcast/RDRA
 tox.org/toxcast/RNR1H2
 tox.org/toxcast/RNUTF2
 tox.org/toxcast/RBARRA
 tox.org/toxcast/RNETS1
 tox.org/toxcast/RNFKB1
 tox.org/toxcast/RNR1D

Bioclipse Visualisation Workbench

The screenshot displays the Bioclipse Visualisation Workbench interface. On the left, a window titled "bursiPos3.mol" shows a chemical structure of a benzimidazole derivative with a hydroxyl group and a nitro group. The nitro group is highlighted with red circles and a red 'X' icon, indicating a failure in the decision support analysis. On the right, a "Decision Support" panel provides a detailed breakdown of the analysis. The panel is organized into a tree view with the following categories and results:

- Uncategorized
 - Lipinski's Rule of Five
 - Failures: 0
- Mutagenicity
 - Bursi exact matches
 - Bursi nearest neighbour
 - Bursi Toxicophores [1 pos]
 - Aromatic nitroso
 - Bursi Signature Significance [1 pos]
 - [C]([C])[N]
- Carcinogenicity
 - CPDB exact matches
 - CPDB nearest neighbour
 - CPDB Signatures

At the bottom of the Decision Support panel, the consensus is displayed as "Consensus: NEGATIVE" with a green checkmark icon.

O. Spjuth, L. Carlsson, M. Eklund, E. Ahlberg Helgee, and Scott Boyer.
Integrated decision support for assessing chemical liabilities. In preparation

Bioclipse Visualisation Workbench

The screenshot displays the Bioclipse Visualisation Workbench interface. The main window shows a chemical structure with several atoms highlighted in green, blue, and brown. A red circle highlights a specific atom in the structure. The interface includes a toolbar with various icons for navigation and analysis. The decision support panel on the right provides a detailed breakdown of alerts and their significance.

Decision Support Panel:

- AHR
 - AHR Signature Alerts
 - AHR Signature Significance [1 neg]
 - [O](=[C])
 - AHR exact matches
 - AHR nearest neighbour
- Carcinogenicity
 - CPDB Signature Alerts
 - CPDB Signature Significance [1 pos]
 - Result: 1.002
 - CPDB exact matches [1 pos]
 - Index 199
 - CPDB nearest neighbour
- Mutagenicity
 - Ames Signature Significance [1 neg]
 - [C]([C][O]=[O])
 - Ames Structural Alerts
 - Ames exact matches [1 pos]
 - 91-64-5
 - Ames nearest neighbour [3 neg]
 - 90-33-5 [tanimoto=0.78]
 - 2107-76-8 [tanimoto=0.76]
 - 26093-31-2 [tanimoto=0.75]

Consensus: NEGATIVE

O. Spjuth, L. Carlsson, M. Eklund, E. Ahlberg Helgee, and Scott Boyer.
Integrated decision support for assessing chemical liabilities. In preparation

Bioclipse Visualisation Workbench - OpenTox

The screenshot displays the Bioclipse Visualisation Workbench interface. The main window shows a chemical structure of a complex molecule with a highlighted epoxide ring. The interface includes several panels:

- Bioclipse N**: A sidebar on the left with a tree view containing 'Sample Data Test1', 'TestBH1', and 'Virtual'.
- Decision Support**: A central panel displaying a list of decision support results:
 - Ames Structural Alerts [1 pos]
 - Epoxide
 - Ames exact matches [no hits]
 - Ames nearest neighbour [3 pos, 1 neg]
 - 26761-45-5 [tanimoto=0.82]
 - 2461-18-9 [tanimoto=0.81]
 - 2461-15-6 [tanimoto=0.73]
 - 5926-90-9 [tanimoto=0.71]
 - OpenTox
 - Caco-2 Cell Permeability <http://www.n>
 - caco2 = -4.548099994659424
 - Lipinski Rule of Five
 - LipinskiFailures = 0.0
 - MolecularWeight
- Properties**: A table at the bottom left showing the following data:

Property	Value
Classification	POSITIVE
Matching atoms	22, 21, 23
Name	Epoxide
Test	Ames Structural Alerts
- 2D-Structure**: A panel at the bottom right for displaying the 2D structure.

O. Spjuth, L. Carlsson, M. Eklund, E. Ahlberg Helgee, and Scott Boyer.
Integrated decision support for assessing chemical liabilities. In preparation

Chemical Space Visualisation (Ches-Mapper)

OpenTox

Ches-Mapper: Chemical Space Mapping and Visualization in 3D

URG TUM

Abstract

Scientific researchers in the field of cheminformatics, chemical datasets. Therefore, the need for visualization of the 3D structure, clustering, and multi-dimensional of similar compounds and consequently arranged in 3D similarity. This intuitively provides essential information allowing easy and understandable access to a large number of different clustering approaches employed in our tool to descriptors of the compounds. These features can be understood the underlying scientific knowledge. As a first part of a given dataset for further analysis.

Build 3D Structure and Extract Features

- Select input dataset
 - Various dataset formats are supported (csv/xml/indri...)
 - Dataset can be directly loaded from the web
- 3D structure is built
 - 3D structure can be built with Chemical Development Kit (CDK) or OpenBabel
 - External libraries like Corina can be plugged in easily
- Extract features
 - Features are required for clustering and embedding
 - Automatic extraction of clusters of descriptors with CDK

Cluster Compounds

- Compounds in the dataset are assigned to subgroups according to their similarity
- Supported cluster algorithms:
 - k-Means Clustering
 - Fixed number of k clusters
 - Random initialization, iterative update of clusters and cluster centroids
 - Hierarchical Clustering
 - Each compound is single cluster
 - Sequentially merge similar clusters
 - Structural Clustering
 - Finds groups that share structural similarity
 - Compounds are assigned to clusters where there exists a common subgraph of sufficient size
- Developers can plug in new cluster algorithms

Home
k_means_cluster_1.sdf
k_means_cluster_2.sdf
k_means_cluster_3.sdf
k_means_cluster_4.sdf
k_means_cluster_5.sdf
k_means_cluster_6.sdf
k_means_cluster_7.sdf
k_means_cluster_8.sdf
k_means_cluster_9.sdf

Spin on/off Wireframe Balls & Sticks

Highlight:

Initial Prototype

Cluster	k_means_cluster_9.sdf
Num molecules	19
LOGP	[2,81; 9,09] 0:5,09
ActivityOutcome_NCTREER	[active(19)]
Species	[rat(19)]
ActivityScore_NCTREER	[80; 100] 0:88,11

Forming chemical feature-based categories

OpenTox

CheS-Mapper: Chemical Space Mapping and Visualization in 3D



Abstract

Scientific researchers in the field of chemoinformatics chemical datasets. Therefore, the need for visual: Our recently developed 3D molecular viewer CheS of best structural clustering, and multi-diverse similar compounds and consequently arranged similarity. This intuitively provides essential information allowing easy and understandable access to a large dataset. The different clustering approaches employed in descriptors of the compounds. These features can understand the underlying scientific knowledge, a part of a given dataset for further analysis.

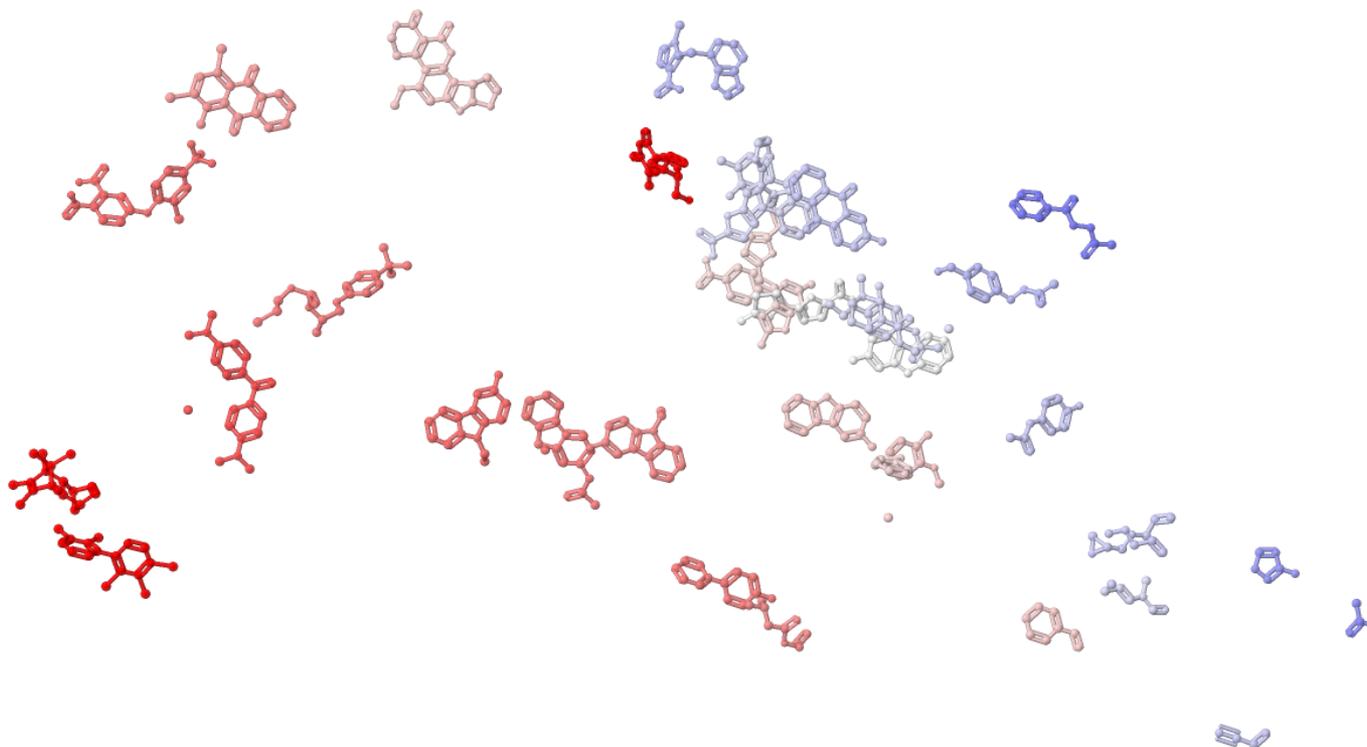
Build 3D Structure Extract Features

- Select input dataset
 - Various dataset formats are supported (csv/xml/indirect...)
 - Dataset can be directly loaded from the web
- 3D structure is built
 - 3D structure can be built with Chemical Development Kit (CDK) or OpenBabel
 - External libraries like Corina can be plugged in easily
- Extract features
 - Features are required for clustering and embedding
 - Automatic extraction of dozens of descriptors with CDK

Cluster Compound

- Compounds in the dataset are assigned according to their similarity
- Supported cluster algorithms:
 - k-Means Clustering
 - Fixed number of k clusters
 - Random initialization, iterative update clusters and cluster centroids
 - Hierarchical Clustering
 - Each compound is single cluster
 - Sequentially merge similar clusters
 - Structural Clustering
 - Finds groups that share structural
 - Compounds are assigned to cluster there exists a common subgraph of size
- Developers can plug in new cluster algorithm

- Java program that comes in two variants:
 - Java Web-Start application (can direct)
 - Local installation that makes use of no
- CheS-Mapper is available at <http://bitbucket.org>



Read-Across Application

Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://localhost:8085/vtox#Categories

http://localhost:8085/vtox#Login

ToxPredict

WELCOME, GUEST

My account
Log out

PREDICT

Search structure
Upload structure
View results

BROWSE

Datasets
Models

READ ACROSS

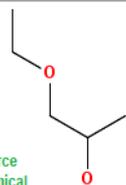
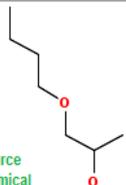
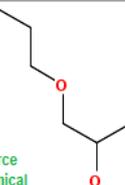
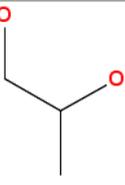
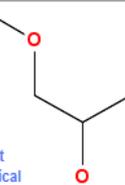
Target compound
Analogues
Categories

Phys Chem properties
Toxicity
Read Across

MY WORKSPACE

My uploads

Page: 0 | Show identifiers Show categories | Assign categories | Download

Property					
Select Structures	Yes	Yes	Yes	No	Yes
CASRN	1569-02-4	5131-66-8	1569-01-3	57-55-6	107-98-2
ChemicalName	1-ethoxypropan-2-ol	1-butoxypropan-2-ol	1-propoxypropan-2-ol	Propylene glycol	1-methoxypropan-2-ol
EINECS	216-374-5	225-878-4	216-372-4		203-539-1
IUPACName					
Categories					
Neutral Organics (alcohol)	YES	YES	YES	YES	YES
Neutral Organics (ether)	YES	YES	YES		YES

Categories

Categories	1	2	3	4	5
Neutral Organics (alcohol)	YES	YES	YES	YES	YES
Neutral Organics (ether)	YES	YES	YES		YES

Developed by Ideaconsult Ltd. 2011

Find: skin | Next Previous Highlight all Match case

Read-Across Application

The screenshot displays the ToxPredict web application interface. At the top, there are navigation tabs: "Property", "Select Structures", "CASRN", "ChemicalName", and "EINECS". Below these are chemical structures for five compounds: 1-butoxypropan-2-ol, 1-propoxypropan-2-ol, 1-ethoxypropan-2-ol, Propylene glycol, and 1-methoxypropan-2-ol. A table of properties follows, with columns for each compound and rows for various physicochemical and toxicological parameters. Below the table is a "Matrix Plot" section with a grid of small plots for each property, each with a "Zoom" button.

Property	1	2	3	4	5
Select Structures	Yes	Yes	Yes	Yes	Yes
CASRN	5131-66-8	1569-61-3	1569-62-4	57-65-6	187-88-2
ChemicalName	1-butoxypropan-2-ol	1-propoxypropan-2-ol	1-ethoxypropan-2-ol	Propylene glycol	1-methoxypropan-2-ol
EINECS	225-878-4	216-372-4	216-374-5		203-039-1
Dissociation_constant					
Model					
pKa-SMARTS	9.80	9.80	9.80	15.52	14.35
Molecular structure					
Molecular weight					
MW	132.20	118.17	104.15	76.09	96.12
Octanol-water_partition_coefficient					
Model					
XLogP	1.12	0.55	0.19	-0.75	-0.23
Reactivity					
Polar surface area					
TopoPSA	29.46	29.46	29.46	40.46	29.46
Electronic descriptors					
CORE-CORE REPLICATION	6503.87	5653.81	4655.69	2697.83	3570.70
EHOMO	-10.54	-10.67	-10.37	-11.06	-10.83
ELECTRONIC ENERGY	-8168.43	-7168.88	-6021.16	-3764.76	-4786.73
ELUMO	2.58	2.60	2.84	2.99	2.68
FINAL HEAT OF FORMATION	-472.91	-455.54	-427.43	-433.85	-414.02
IONIZATION POTENTIAL	10.54	10.67	10.37	11.06	10.83
MOLECULAR WEIGHT	132.20	118.18	104.15	76.10	96.12
NO. OF FILLED LEVELS	28.00	25.00	22.00	16.00	19.00
TOTAL ENERGY	-1664.56	-1515.07	-1365.47	-1066.93	-1216.03
Hydrogen Bond acceptors					
nHBAcc	2.00	2.00	2.00	2.00	2.00

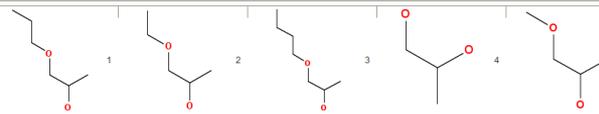
Read-Across Application

Mozilla Firefox
 http://localhost:8085/vtox#Toxicity
 chembl id
 http://localhost:8085/vtox#Login

ToxPredict

WELCOME, GUEST
 My account
 Log out
 PREDICT
 Search structure
 Upload structure
 View results
 BROWSE
 Datasets
 Models
 READ ACROSS
 Target compound
 Analogues
 Categories
 Phys Chem properties
 Toxicity
 Read Across
 MY WORKSPACE
 My uploads

Property



1 2 3 4

Carcinogenicity

Dataset	1	2	3	4
CAS				57-55-6
Canc				
Mouse_Female_Canc				ND
Mouse_Female_NTP				ND
Mouse_Male_Canc				ND
Mouse_Male_NTP				ND
Rat_Female_Canc				
Rat_Female_NTP				ND
Rat_Male_Canc				
Rat_Male_NTP				ND
Reference				CPDB
SAL				

Model

Model	1	2	3	4
Potential S. typhimurium TA100 mutagen based on QSAR	NO	NO	NO	NO
Potential carcinogen based on QSAR	NO	NO	NO	NO
Structural Alert for genotoxic carcinogenicity	NO	NO	NO	NO
Structural Alert for nongenotoxic carcinogenicity	NO	NO	NO	NO
Unlikely to be a S. typhimurium TA100 mutagen based on QSAR	NO	NO	NO	NO
Unlikely to be a carcinogen based on QSAR	NO	NO	NO	NO

EPA Integrated Risk Information System (IRIS) Toxicity Review Data

Inhalation_RIC_Assessed				1.00
Inhalation_RIC_Confidence				Medium
Inhalation_RIC_CriticalEffects				mild reversible sedation
Inhalation_RIC_Notes				NOEL (No observed adverse effect level)-HEC (Huma
Inhalation_RIC_mg_per_m3				2.00
Inhalation_RIC_mmol_per_m				0.02
Inhalation_StudRoute				
Inhalation_UnitRisk_Assesse				0.00
Inhalation_UnitRisk_microg_l				
Inhalation_UnitRisk_micromc				

Physico chemical properties >> Boiling point

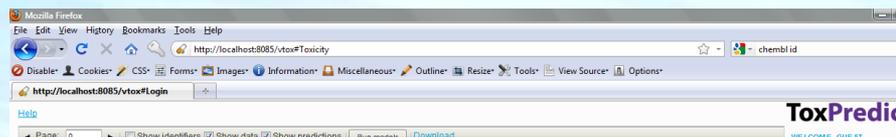
Dataset	Value
BP	119.00
Boiling Point Pressure	
CAS	107-98-2
Error	-2.45
EstBP	116.55
ExpBP	119.00
NAME	1-METHOXY-2-PROPANOL

Skin sensitisation

Model	1	2	3	4
Alert for Acyl Transfer agent identified.	NO	NO	NO	NO
Alert for Michael Acceptor identified.	NO	NO	NO	NO
Alert for SN2 identified.	NO	NO	NO	NO
Alert for SN4 identified.	NO	NO	NO	NO
Alert for Schiff base formation identified.	NO	NO	NO	NO
No skin sensitisation alerts identified.	YES	YES	YES	YES

Matrix Plot Show
 http://localhost:8085/amb1/dataset/R11189

Read-Across Application



Carcinogenicity						
Dataset						
CAS					57-55-6	
Canc					YES	
Mouse_Female_Canc					ND	
Mouse_Female_NTP					ND	
Mouse_Male_Canc					ND	
Mouse_Male_NTP					ND	
Rat_Female_Canc					YES	
Rat_Female_NTP					ND	
Rat_Male_Canc					YES	
Rat_Male_NTP					ND	
Reference					CPDB	
SAL					YES	
Model						
Potential S. typhimurium TA100 mutagen based on QSAR	NO	NO	NO	NO	NO	NO
Potential carcinogen based on QSAR	NO	NO	NO	NO	NO	NO
Structural Alert for genotoxic carcinogenicity	NO	NO	NO	NO	NO	NO
Structural Alert for nongenotoxic carcinogenicity	NO	NO	NO	NO	NO	NO
Unlikely to be a S. typhimurium TA100 mutagen based on QSAR	NO	NO	NO	NO	NO	NO
Unlikely to be a carcinogen based on QSAR	NO	NO	NO	NO	NO	NO
EPA Integrated Risk Information System (IRIS) Toxicity Review Data						
Inhalation_RfC_Assessed						1.00
Inhalation_RfC_Confidence						Medium
Inhalation_RfC_CriticalEffects						mild reversible sedation

Identified	NO	NO	NO	NO	NO
Alert for SN2 identified	NO	NO	NO	NO	NO
Alert for SN4 identified	NO	NO	NO	NO	NO
Alert for Schiff base formation identified	NO	NO	NO	NO	NO
No skin sensitisation alerts identified	YES	YES	YES	YES	YES

Matrix Plot [Show](#)
<http://localhost:8080/ambicid/dataset/R11188>

Ontology - automating consistency

We have defined an ontology based on the OWL (Web Ontology Language) for toxicological endpoints which is in line with current ECHA REACH guidance.

Using this ontology, each attribute in a toxicological dataset can be associated with an entry to the ontology, therefore allowing a unique mapping between endpoints in various and heterogeneous datasets.

The mapping of chemical compound properties, stored in the OpenTox prototype database, with the endpoints ontology, and the information which properties are predicted by models, available via the OpenTox model service, is used to automatically recognise which endpoints have predictive models available, and ensures consistency of the used endpoint terminology across the set of distributed OpenTox services.

OpenToxipedia



Barry Hardy Log out Quicktools Site Setup Help

Site Map Accessibility Contact Data

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Home Toxicity Prediction OpenTox Blog People Partners Development OpenToxipedia
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OpenToxipedia

by Barry Hardy — last modified Sep 03, 2009 01:09 PM

OpenTox Community Resource for Toxicology Vocabulary and Ontology

OpenTox is supporting the creation and curation of OpenToxipedia, a community-based predictive toxicology knowledge resource. All members of the community are welcome to provide entries, suggested definition edits or additional information to entries in the resource.

OpenTox is supporting the application and development of the **ToxML** standard for representation of toxicology data, the **OECD principles for (Q)SAR model validation**, and the use of the **OECD HT** standard for regulatory reporting purposes.

OpenToxipedia provides here a Vocabulary Resource of toxicology terminology. We hope you find the resource useful and consider contributing to terms and their content.

Guidance for Vocabulary Resource entries



www.opentox.org/opentoxipedia

A Toxicology Ontology Roadmap

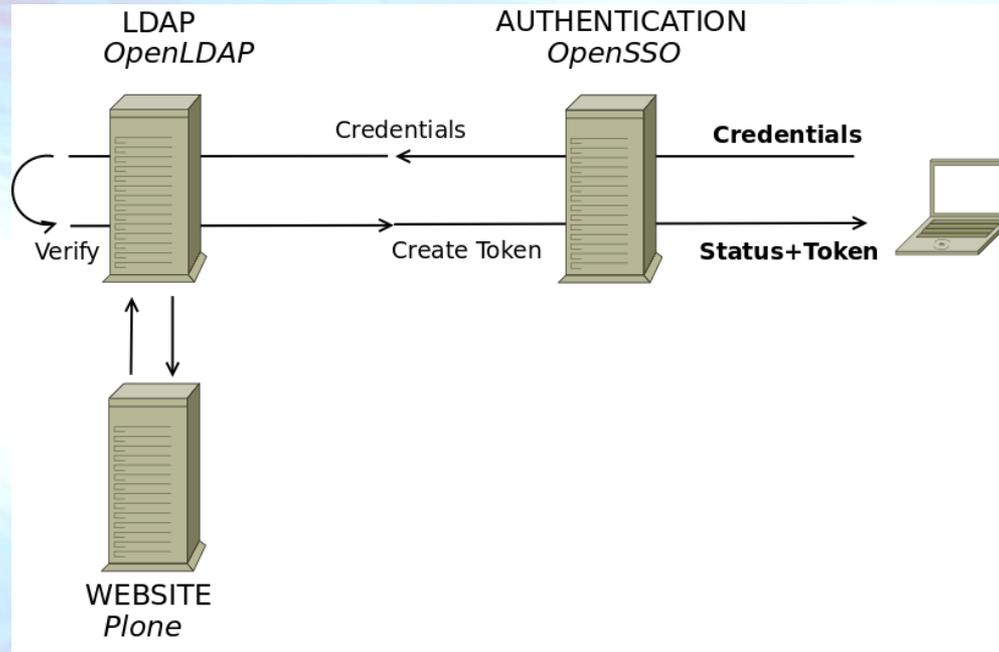
In Preparation by: Barry Hardy (Douglas Connect and OpenTox), Ian Dix (AstraZeneca & Pistoia Alliance), Sherri Matis-Mitchell (AstraZeneca), David Cook (AstraZeneca), David Heard (Novartis), Dominic Clark (EMBL-EBI), John Overington (EMBL-EBI), Philip Judson (Lhasa), David Watson (Lhasa), Anne Hersey (EMBL-EBI), Andrew White (Unilever), Loca Toldo (Merck KGaA), Gordana Apic (Cambridge Cell Networks), Imran Shah (US EPA), Chihae Yang (Altamira), Dave Bower (Leadscope), Ola Spjuth (Univ Uppsala), Janna Hastings (EMBL-EBI), Philip Carthew (Unilever), ----

Based on Proceedings from the **Toxicology Ontology Roadmap Workshop**
EMBL-EBI Industry Programme Workshop
16 -17th November 2010, Hinxton, UK

Controlling Access to Confidential Information

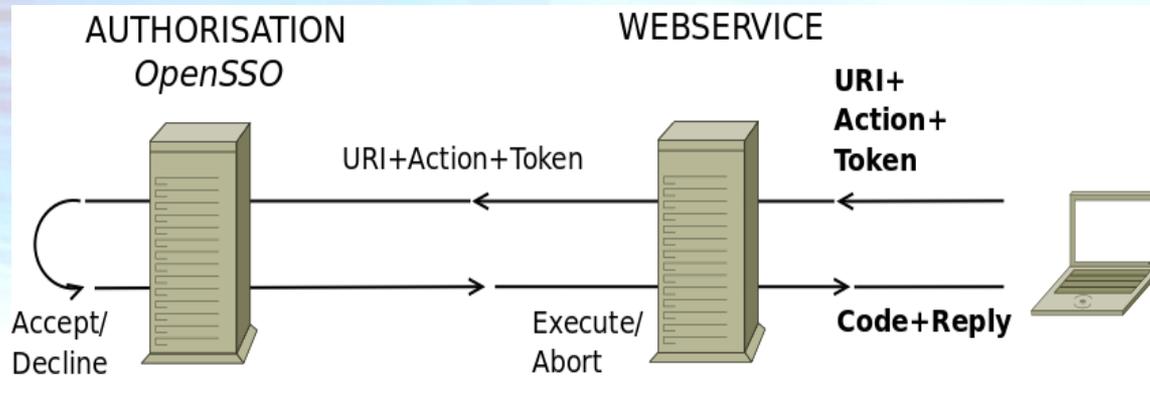
- OpenTox makes resources available through **URIs**
- OpenTox provides facilities to protect confidential information located at **URIs**. Two tasks are involved here:
 - **Authentication**: Confirming the identity of the user requesting access
 - **Authorisation**: Granting the confirmed identity access according to a set of restrictions described in policies

Authentication



- Registered users are instantly available as potential users of OpenTox web services
- Users receive a token upon service request

Authorisation

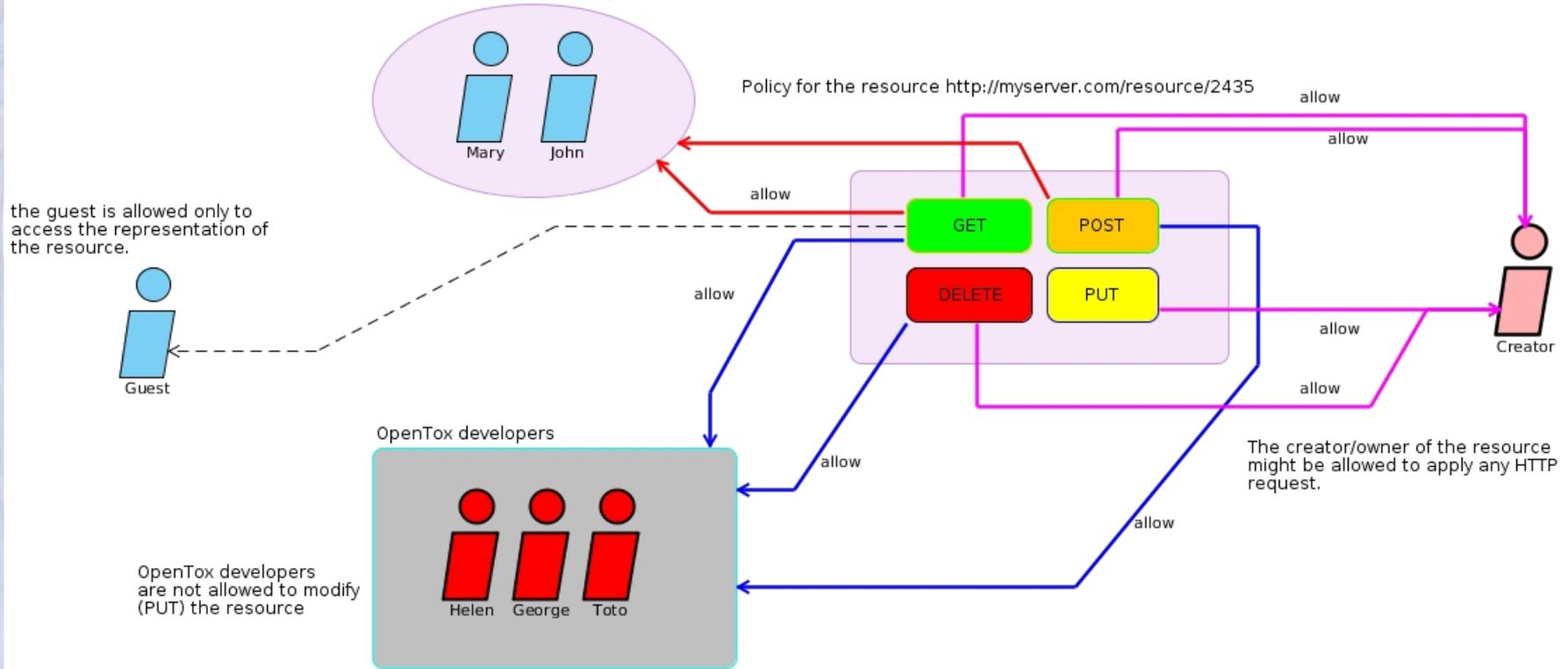


- Tokens encode user identity
- Tokens are valid for a certain time period only (customizable)
- The triplet URI+Action+Token makes up the call to be authorised
- All messages are encrypted (SSL)
- Resource Owners create and modify policies defining access rules

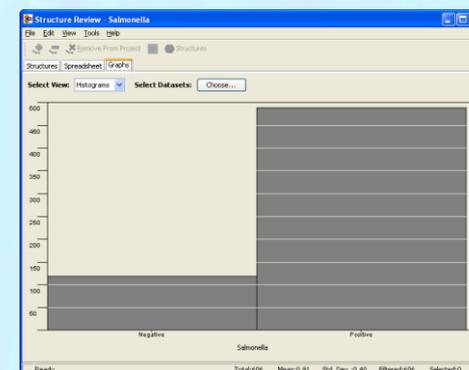
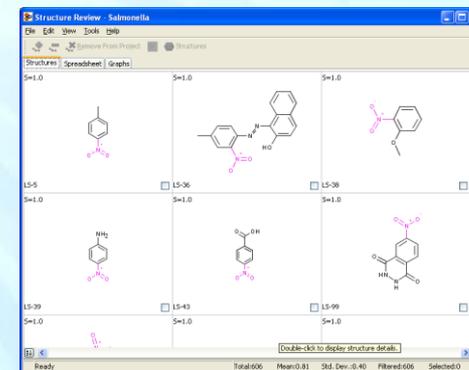
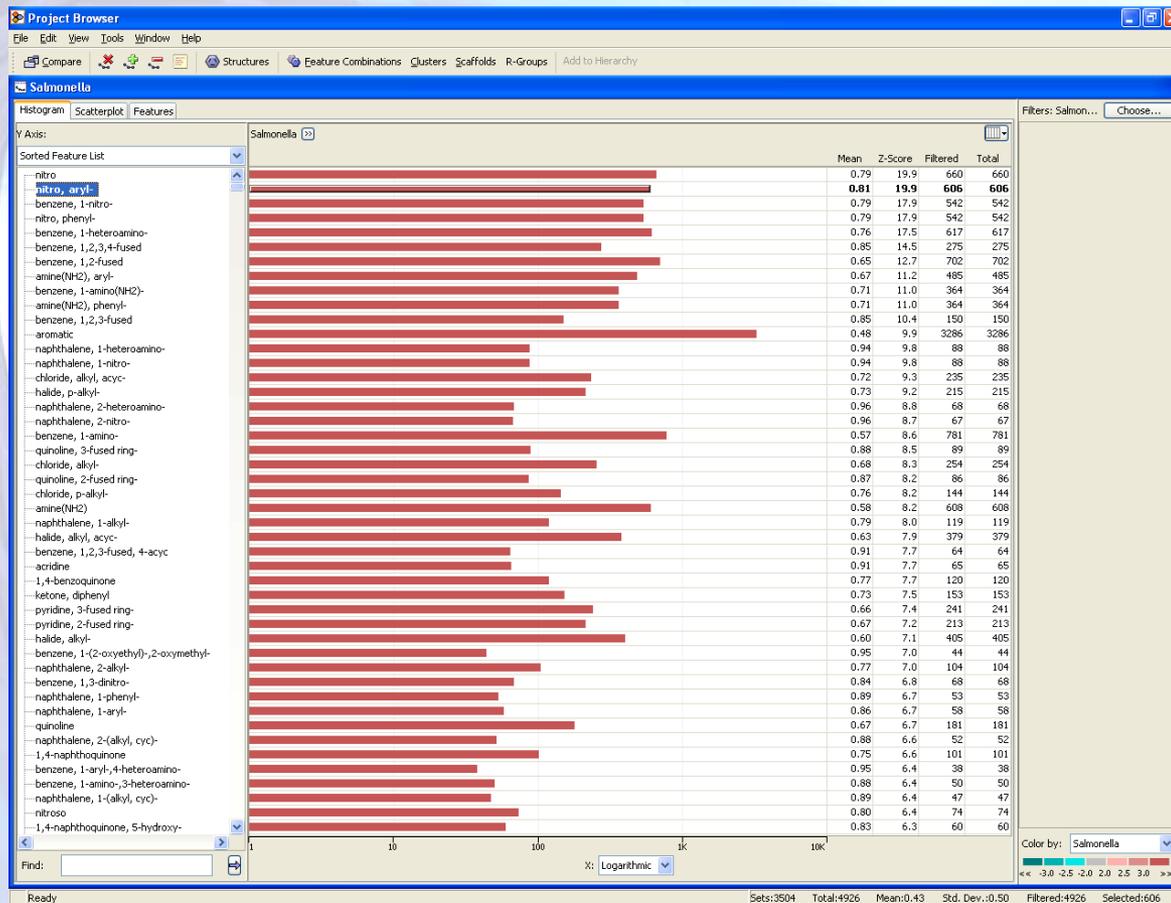
Policies

Visual Paradigm for UML Community Edition [not for commercial use]

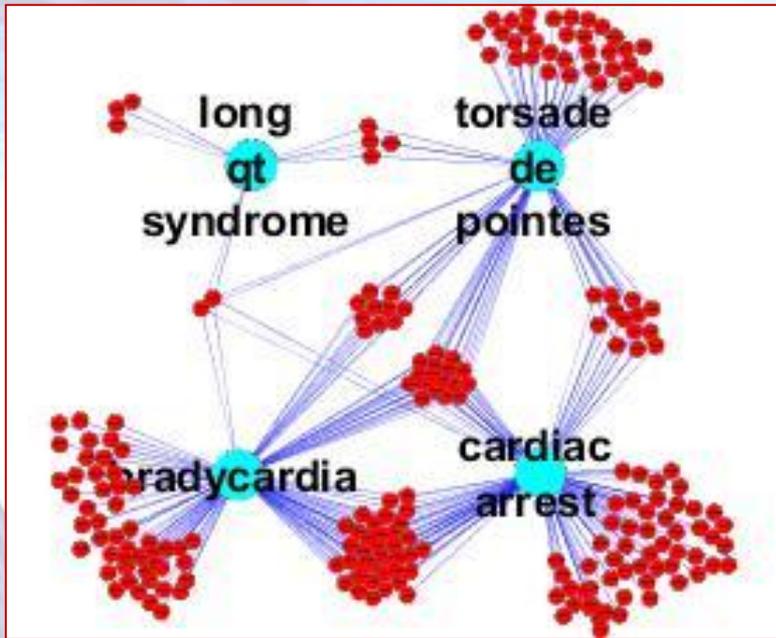
Chemistry Lab Staff



OpenTox - Leadscope Integration



Analysis of Adverse Events Based on Pharmacological Activity



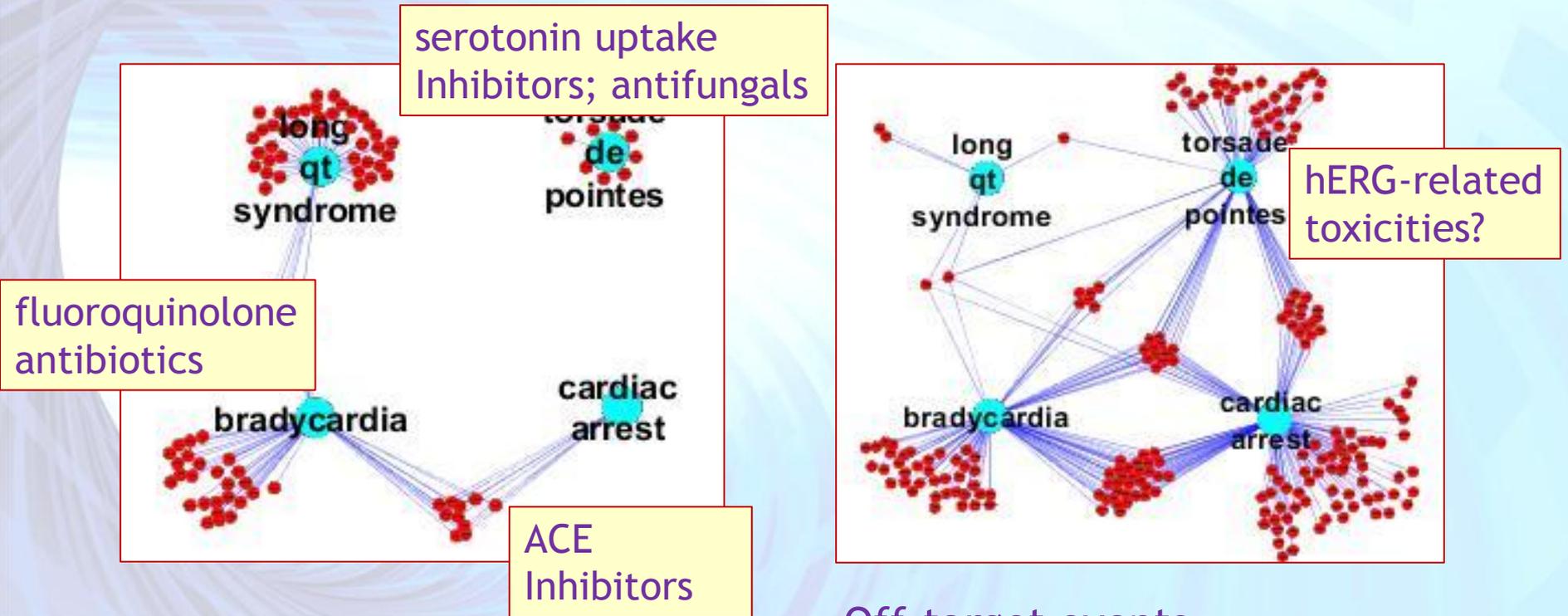
- Cardiac adverse events
- Related to hERG ion channel?

cyan = adverse event, red = drug
lines define links

- Question addressed:
 - Are the adverse events a function of inhibiting the pharmacological target?
 - Or is the adverse event due to an off-target activity?



Example: Cardiac Adverse Events



On-target events

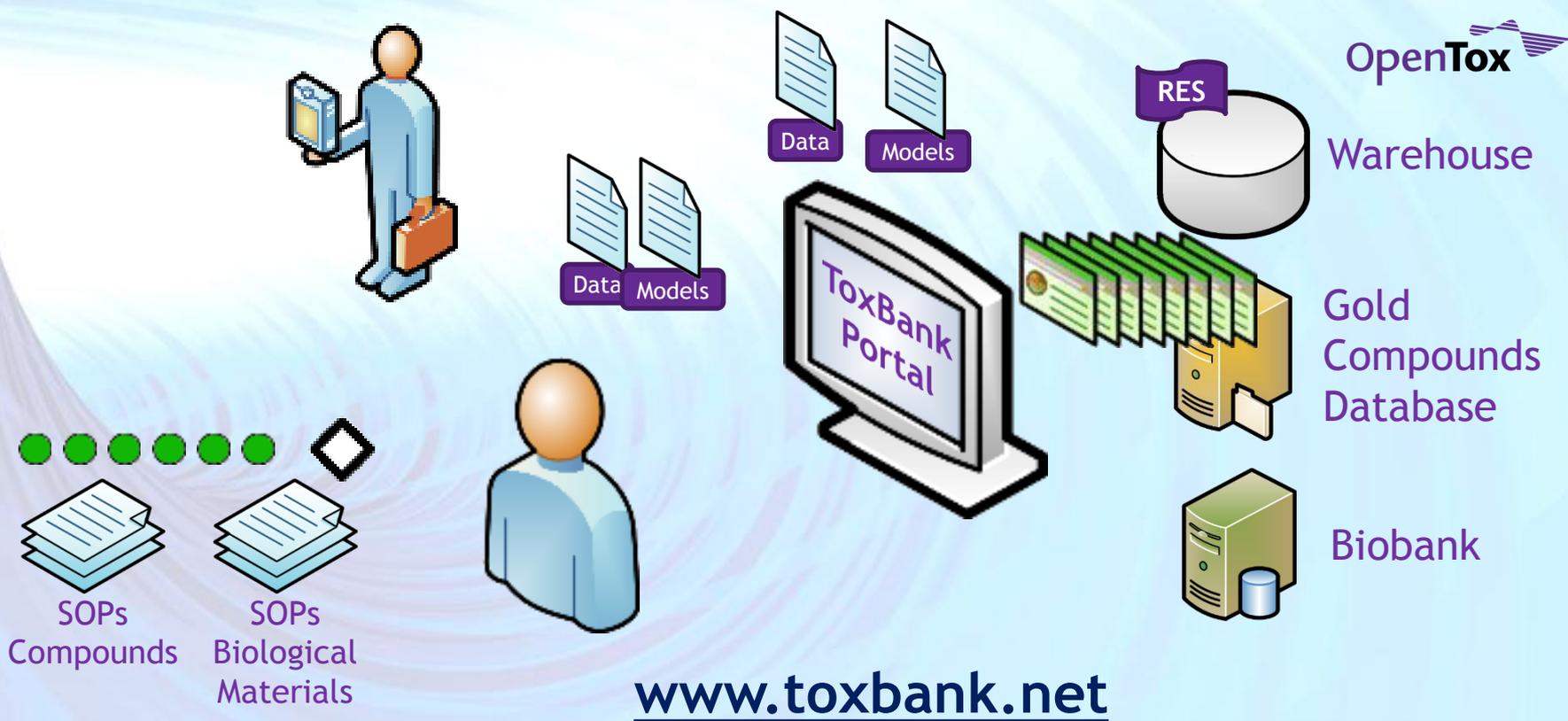
cyan = adverse event, red = drug
lines define links

Off-target events

PHARMATROPE

Our Infrastructure Vision for ToxBank supporting all steps of Predictive Toxicology Research based on Alternative Testing methods

Users access compounds, biological materials, data and models for experimental planning and integrated analysis of experimental results



Collaborative Research Framework Integration

Rescentris CERF v2.6.0

Sessions Collections Search Help

CERF Collections

- NB-Experiments-01
- NB260
 - Notebook Section
 - Experiments-02
 - Anti-erbB2 treatment induces cardiotoxicity
 - 9. Differential role of ICAM ligands
 - 10. Assay Development
 - 13. R-methylanthraquinone Synthesis
 - Notebook Section-03
 - 11. Microarray Studies
 - 12. Excel Chem research project
 - 14. Differential role of ICAM ligands-2
- Cancer Research 11
- JSpitzner-038
- Contract Neurotoxicology Research - 023
- Lab Project Research-003
- InstrumentData
- Experiment Project
- Experiments 2006
- Protein Analysis
- Lead ID-1034
- Functional Genomics-07-11-04
- DNA Methylation Studies-03
 - Role of DNA Methylation in Gene Expression
 - 1. Experimental Aims
 - 2. Materials and Methods
 - 3. Experimental Procedures
 - Protocol I.doc
 - Protocol II.doc
 - Protocol III.doc
 - Protocol IV.doc
 - 4. Results
 - Annotated results
 - Gel Images
 - Sequencing Gel 1.jpg
 - Sequencing Gel 2.jpg
 - Gel 3.jpg
 - Spreadsheets
 - Raw Data_1.xls
 - RUIL2.XLS
 - 5. Conclusions

- ispitzner

My CERF Resource Info: 14. Differentia Local Filesystem Notebook Viewer

NB260 > Notebook Section-03 > 14. Differential role of ICAM ligands-2

14

A. CD4+ (24 hrs)

Control
10 ng
100 ng
1000 ng

B.

Cleaved Caspase 3

Median Fluorescence

24 hrs
48 hrs
72 hrs

Cleaved Caspase-3
48 hrs, 100 ng stimulant

CD3/CD28
CD3/CD28/ICAM-1
CD3/CD28/ICAM-2
CD3/CD28/ICAM-3

Fig. 1. Stimulation of LFA-1 through ICAM-2 and ICAM-3 in the presence of CD3/CD28 co-stimulation does not activate caspase-3. (A) Intracellular staining of cleaved-caspase 3 in cells treated with ICAM-1, ICAM-2, ICAM-3, CD3, CD3/CD28, CD3/CD28/ICAM-1, or CD3/CD28/ICAM-2, or CD3/CD28/ICAM-3. Naïve T cells were stimulated in 96-well coated plates and stained for CD4-PercpCy5.5 and intracellular cleaved-caspase-3-PE at 24 hrs.

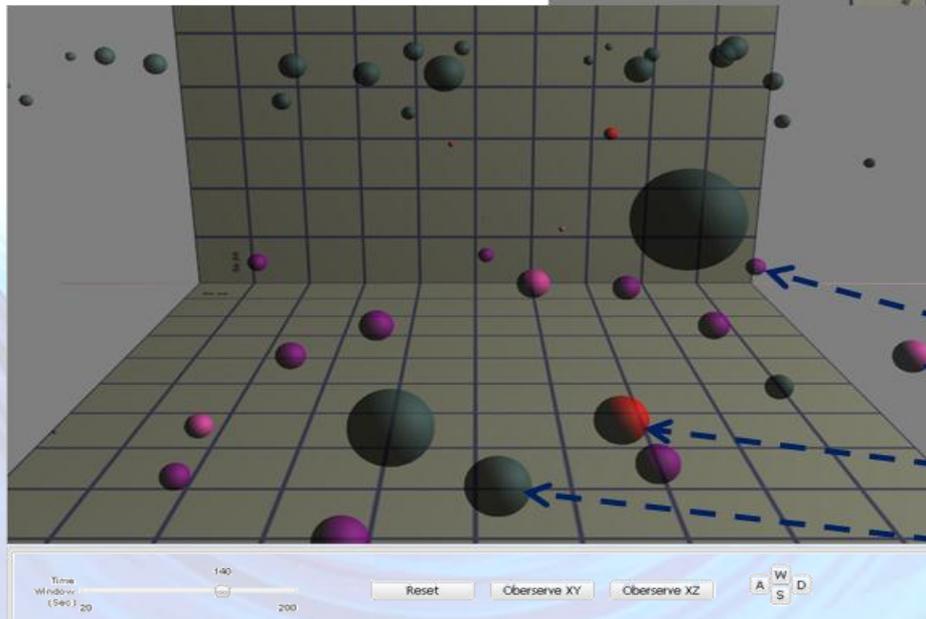
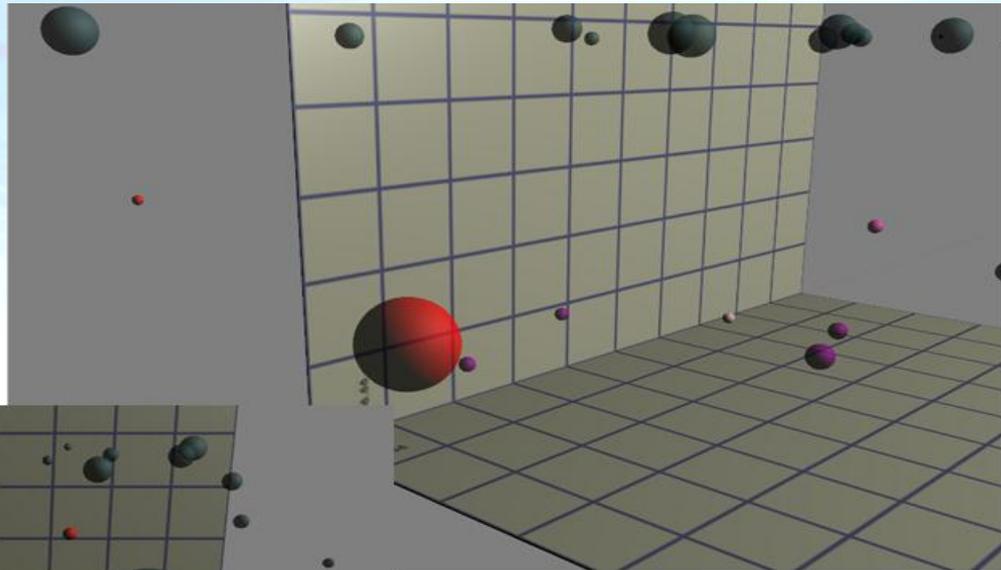
Controlled
Vocabularies

Visualisation

Collaborative
Electronic Notebook
(CERF)

Processing Complex Events Stream

Model 1	Model 2	Model 3		Assay 1	Assay 2	Assay 3	
1	0	1		-	-	-	



Reset Observe XY Observe XZ A W S D

Showing	Symbol	PatternID	PatternName
<input checked="" type="checkbox"/>		carbon	Carbon
<input checked="" type="checkbox"/>		china	China

Symbol **Pattern Name**

- DOCK stopDOCK
- ADME stopADME
- TOX stopTOX

Event Driven Weight of Evidence

CERF Client v4.0.0 - Logged in to Enterprise as jspitzner

Sessions Collections Bookmarks Search Tools Help

Project: Project-1001 Subject: Subject-1001 Compound Set: All Compound Sets Refresh Show Filters New Project New Subject New Compound Set New Compound Add Result

Results 1 to 100 of 197

Compound ID	Phore	VS	Dock	Dock 2	Binding Prediction Stoplight	QSAR ADME	QSPR ADME	ADME Prediction Stoplight	Binding + ADME Prediction Stoplight	Logic Based Tox	Limited Free Energy Tox	Toxicology Prediction Stoplight	Binding + ADME + Tox Prediction Stoplight	Saturation Binding Assay	Protein-DNA Binding Assay	Binding Assay Stoplight	In Vitro Toxicology Assay	In Vivo Toxicology Assay	Toxicology Assay Stoplight	Binding + Tox Assay Stoplight	Final Stoplight	
UC0000353			0	0				0.0	-6.0999999													
UC0000862								-10.47	-10.8													
UC0000864								-10.2	-10.9													
UC0000884								-9.1400003	-10.6													
UC0000885								-9.1400003	-10.5													
UC0000886								-9.41	-10.6													
UC0000921								-10.91	-9.1000004													
UC0001349								-9.9799995	-11.2													
UC0001350								-9.96	-11.2													
UC0001500								-9.3299999	-9.3999996													
UC0001501								-9.5699997	-9.6000004													
UC0001623								-9.4899998	-9.1000004													
UC0001624								-9.4899998	-9.1000004													
UC0001699								-12.2	-10.9													
UC0001700								-9.9899998	-9.8000002													
UC0001702								-13.37	-9.6000004													
UC0001703								-10.61	-10.7													
UC0001743								-9.29	-9.1000004													
UC0001775								-9.7700005	-9.1000004													
UC0001875								-9.84	-9.2													
UC0001987								-9.7700005	-9.1999998													
UC0002838								-9.1999998	-9.8999996													
UC0002854								-10.09	-10.0													
UC0003266								-9.4799995	-9.8000002													
UC0003454								-9.1899996	-10.0													
UC0003835								-9.1000004	-9.8000002													
UC0003867								-10.25	-9.3999996													
UC0003923								-9.7200003	-9.8000002													
UC0003941								-10.52	-9.3000002													
UC0003973								-9.3100004	-9.1999998													

Aggregate Resource

Project Subject Compound Set Compound

Title: Project-1001

Status ?

Edit Status: Versionable
 Owner: jspitzner
 My Role: Notebook Creator
 Closed: No
 Checked Out: No
 Visibility: Shared
 Id: 26203 (Federation: 43214, Server: 801)

Metadata ?

Title: Project-1001

Submission/Modification

Resource Type: Drug Design Project
 Creation Date: Oct 21, 2010 2:57:10 PM
 Last Update: Oct 21, 2010 2:57:10 PM
 Contributor: Jeff Spitzner

Relations and Annotations ?

Comment Tag Browse Tags

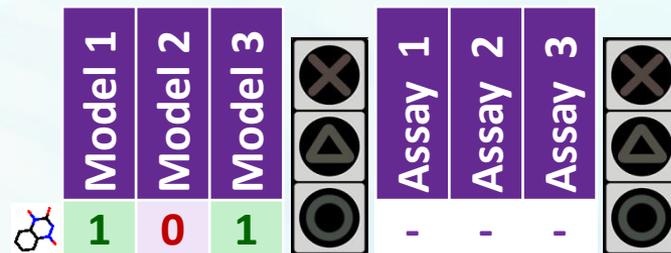
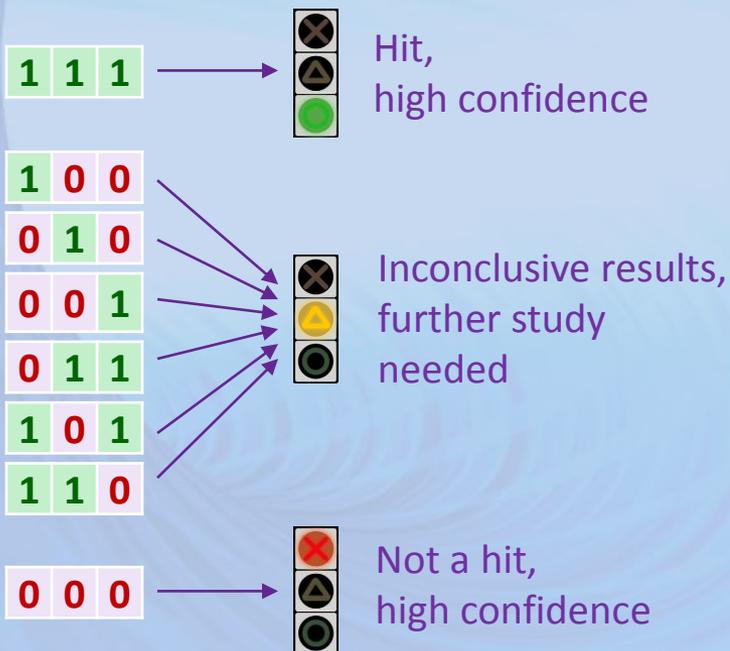
Previous Next Results per page: 100

Event Driven Weight of Evidence

collaboration
MODERATOR

Consensus Rule
Editor

Recommendation Rules:



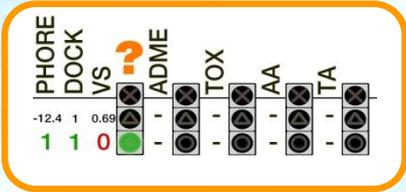
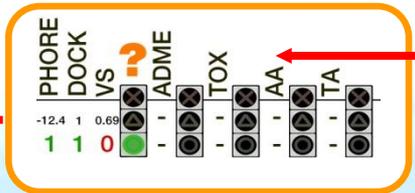
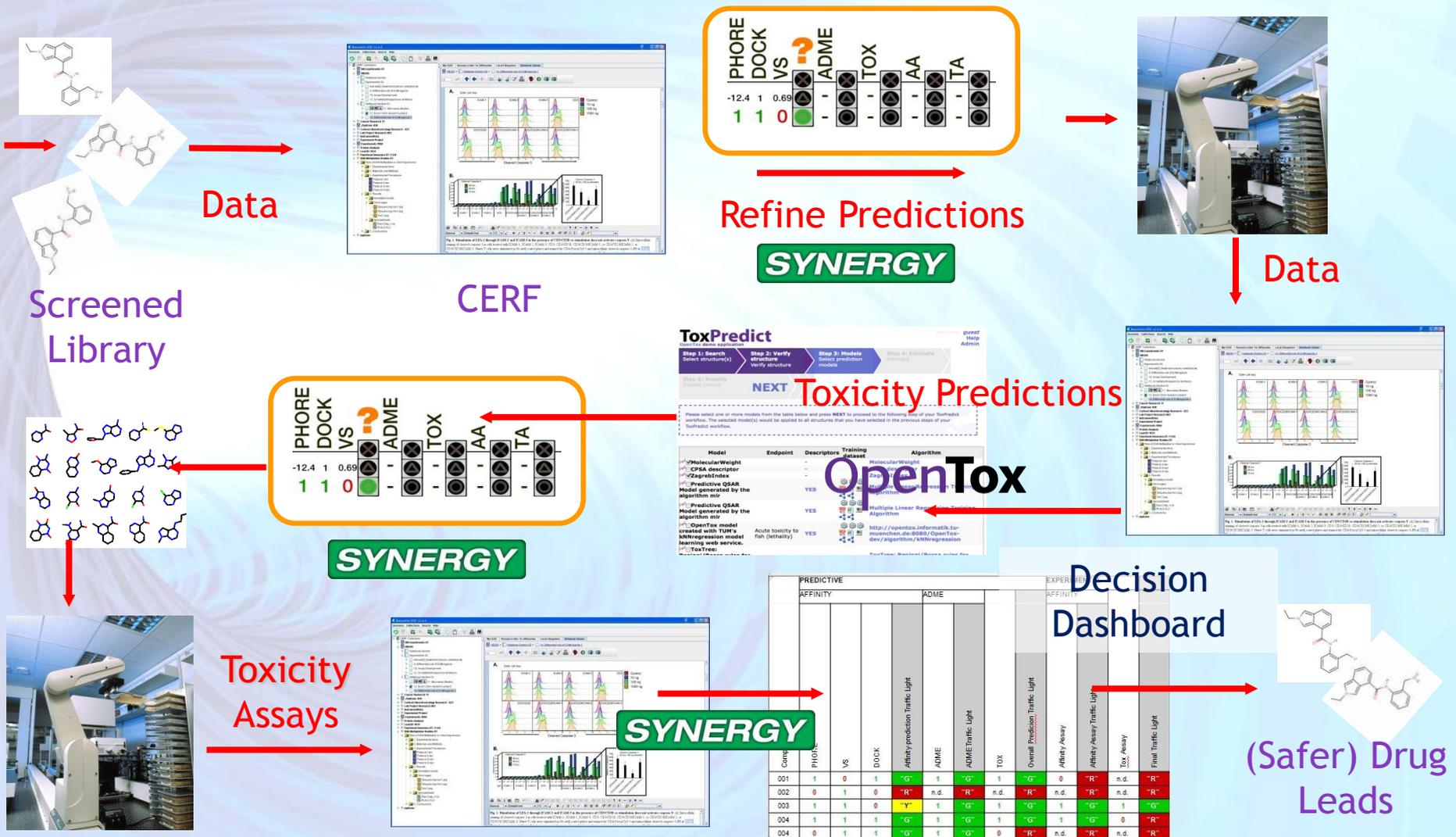
Synergy



OpenTox



Synergy Drug Design Collaboration Pilot



ToxPredict

Step 1: Search (Select structure(s)) → Step 2: Verify (Select prediction model) → Step 3: Models (Verify structure)

OpenTox

Model Endpoint Descriptors Training Dataset Algorithm

- ✓ Molecular Weight
- ✓ ClogP descriptor
- ✓ Zagreb Index
- ✓ Predictive QSAR
- ✓ Predictive QSAR
- ✓ OpenTox model created with Tox's MNR regression model learning web service.
- ✓ ToxTree

Decision Dashboard

Comp	PREDICTIVE AFFINITY						EXPERIMENTAL AFFINITY					
	PHORE DOCK	VS	DOCK	Affinity-prediction Traffic Light	ADME	ADME Traffic Light	TOX	Overall Precision Traffic Light	Affinity Assay	Affinity Assay Traffic Light	Tox Assay	Final Traffic Light
001	1	1	1	G	1	G	1	G	1	G	n.d.	R
002	0	1	0	R	n.d.	R	n.d.	R	n.d.	R	n.d.	R
003	1	1	1	Y	1	G	1	G	1	G	0	R
004	1	1	1	G	1	G	1	G	1	G	0	R
004	0	1	1	G	1	G	0	R	n.d.	R	n.d.	R

What are the benefits of OpenTox?

Through using components, open source and open, standard interfaces the OpenTox architecture enables:

- numerous applications in (Q)SAR, Read Across, reporting, metabolism prediction, etc. to be developed
- reliable integration of multiple applications
- easier retrieval and integration of data from multiple resources
- advancement of the *in silico* predictive toxicology field
- new improved algorithms and models to be built which can be used for REACH endpoints
- The integration of (Q)SAR into workflows eg. for Weight of Evidence

OpenTox Workshop with 90 Participants in Rhodes

Rhodos, Greece
Sept. 2010
OpenTox 3rd meeting

EuroQSAR 2010

**Ca. 90 participants engaged in
using a variety of OpenTox
applications**



OpenTox InterAction Meeting

Innovation in Predictive Toxicology

Modeling, Applications, REACH, Risk Assessment

9-12 August, 2011

Technical University of Munich, Germany

Registration: Free but limited to 100 attendees
<https://www.surveymonkey.com/s/opentox2011>

Abstracts by: 30 April 2011, **Posters:** 30 June 2011

Bursary Award: three abstracts will be selected for travel & accommodation awards (by 30 April 2011)

More Information at:
www.opentox.org/meet/opentox2011



OpenTox and REACH Workshop

9 August 2011, Technical University Munich

Practical Workshop on how OpenTox satisfies REACH requirements:

- 1 Supporting Information Gathering & Evaluation
- 2 Data Sourcing and Integration
- 3 (Q)SARS (including Applicability Domain, Validation, QMRF, QPRF reporting, Reliability, Confidence)
- 4 Categories and Read Across
- 5 Weight of Evidence
- 6 Predicting Metabolites
- 7 Achieving Harmonisation through Ontologies

An extensive manuscript will be prepared and submitted for publication.

Collaborating Partners

In Silico Toxicology,
Switzerland

Ideaconsult,
Bulgaria

Istituto Superiore
di Sanità, Italy

Technical University
of Munich, Germany

Douglas Connect,
Switzerland
(Coordinator)



Albert Ludwigs University
Freiburg, Germany

National Technical
University of Athens,
Greece

Fraunhofer Institute
for Toxicology &
Experimental Medicine,
Germany

David Gallagher, UK

Institute of Biomedical
Chemistry of the Russian
Academy of Medical
Sciences, Russia

Seascope Learning &
JNU, India

Our Funding Support...

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Project Reference Number Health-F5-2008-200787 (2008-2011).

For more information, visit
www.opentox.org

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