

OpenTox

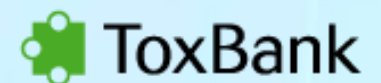
OpenTox USA 2013

29 October

North Carolina Biotech Center

Raleigh-Durham

Barry Hardy (Douglas Connect)



# Thank you -

For organising ...

For preparing ...

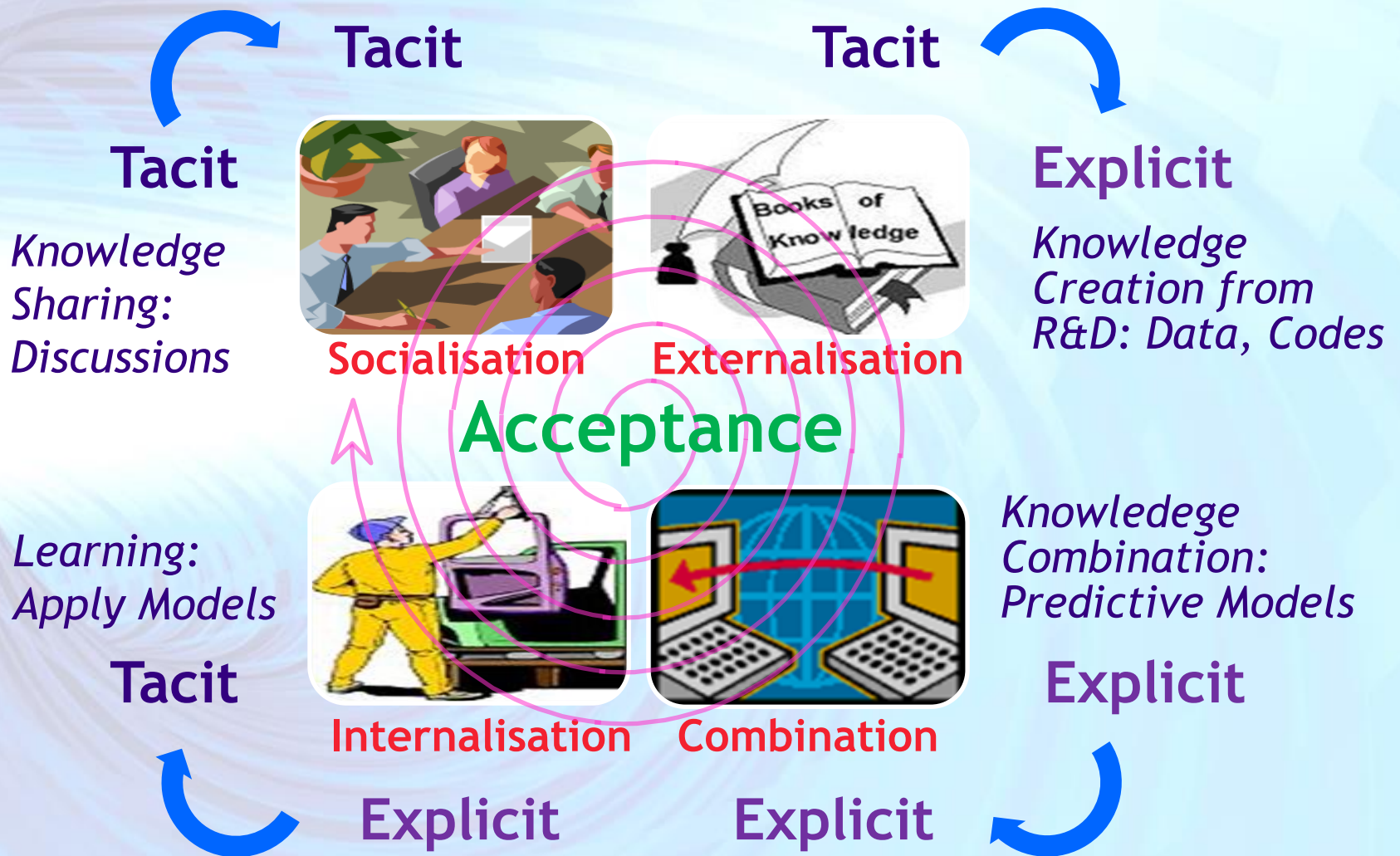
For coming ...

For overcoming shutdown paralysis ...

For being open to participating in new developments and adventures ...



# Knowledge-Oriented Framework



# Knowledge Sharing



18M


OpenTox 



# OpenTox Euro 2013



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## OpenTox Euro 2013

 OpenTox InterAction Meeting

**Innovation in Predictive Toxicology**

Open Infrastructure and Application Development, Integrated Data Analysis, Visualisation,  
Cheminformatics, Bioinformatics, Systems Biology

*Organised in Collaboration with ToxBank*  ToxBank

**30 September - 2 October 2013**

**Johannes Gutenberg University of Mainz, Mainz, Germany**

## What is OpenTox?

We are an Open Knowledge Community!

We collaborate, solve problems and create the best solutions we can together.

We learn from each other .. and enjoy it.

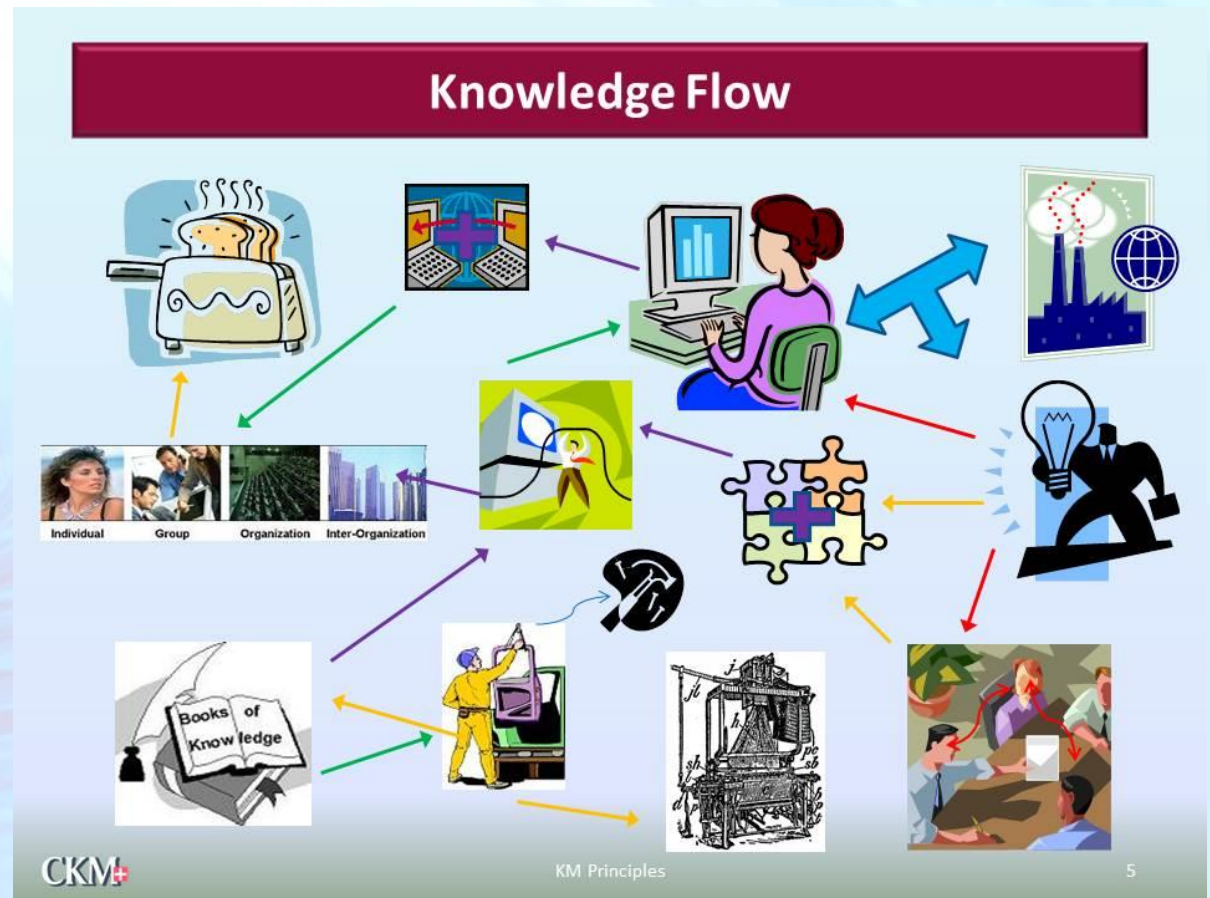
We accelerate knowledge flow & innovation.

**Supported by a 21st Century  
Computer Science for Predictive  
Toxicology and Safety Assessment that  
we develop together**



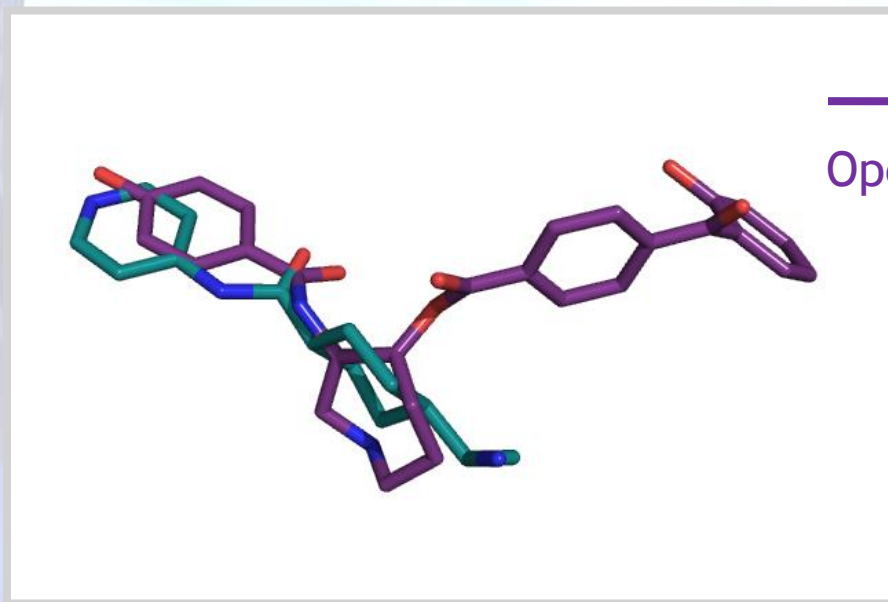
# Goals for next year for OpenTox

- Implement Expanded Data Foundation  
(based on Consensus Open Specifications)
- Leverage Foundation for Applications and Impact
- Develop Scientific and Business Ecosystem  
Accelerate Knowledge Flow



# Predictive Toxicology Challenge & Use Case

## Input Structure



→  
OpenTox

## Out - Toxic or Not?

- LD50
- Liver Toxicity
- Secondary Metabolites
- Bioavailability
- Mutagenicity
- Carcogenicity
- Reproductive Toxicology
- Skin Irritation
- Aqua Toxicity
- Combined predictions for arrays of multiple end points

# Challenges to Interoperating Resources & Applications

- Database silos
- Missing information
- Varying quality
- Hard to integrate data
- Hard to integrate models
- No common framework
- Lack of consensus on working standards
- Lack of validation
- Complex subject
- Application difficult
- Lack of transparency
- Interdisciplinary collaboration

# OpenTox is an Integrating Framework

## Framework

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

## Applications

- Toxicolog, Biolog, Chem - ists
- Computational Scientists
- Interfaces for new analysis, development & integration

## Interoperability

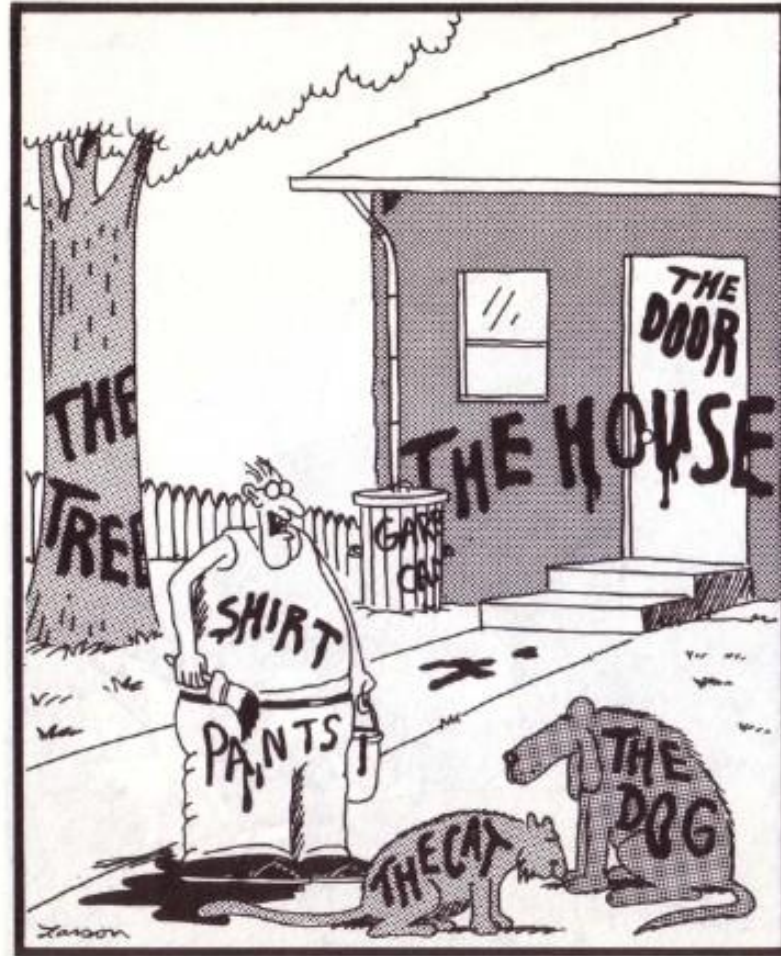
- Promote Standards
- Core Open Source Components
- Support Ontologies & Integration of Multiple Resources

# Interacting Components create Solutions



Adaptor Solution in Jeddah, 2008

# Semantic Reflections



"Now! ... *That* should clear up a few things around here!"

# OpenTox committed to creating a Semantic Web for Predictive Toxicology (*with its API 1.1 development in 2009*)

Linked Data is a term used to describe the exposing, sharing, and connecting of data on the Semantic Web using:

**URIs** a generic means to identify entities in the world

**HTTP** a simple yet universal mechanism for retrieving resources

**RDF** a generic graph-based data model with which to structure and link data

Linked Data needs:

1. Provision of a **URI** that describes a Data Resource
2. Use of **HTTP** to retrieve useful data from the **URI**
3. A Data Format described with standardised semantics (so relationships are enabled) e.g. **RDF**
4. Data should provide links to other Data (through **URIs**)

Linked Data approach can also be applied to other resource types e.g., for algorithms or models as done in OpenTox... **Linked Resource** approach enables Knowledge Creation, Combination and Analysis



DBpedia = Linked Data approach applied to Wikipedia

# The OpenTox Framework (reported 2010)

## 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 Gloriovova, 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](http://www.jcheminf.com/content/2/1/7)



# Overview of Application Programming Interfaces

v1.1

**Dataset**

GET  
POST  
PUT  
DELETE

**Feature**

GET  
POST  
PUT  
DELETE

**Compound**

GET  
POST  
PUT  
DELETE

**AppDomain**

GET  
POST  
PUT  
DELETE

**Model**

GET  
POST  
PUT  
DELETE

**Algorithm**

GET  
POST  
PUT  
DELETE

**Report**

GET  
POST  
PUT  
DELETE

**Validation**

GET  
POST  
PUT  
DELETE

**Ontology**

GET  
POST  
PUT  
DELETE

v1.3?

## Investigate

GET  
POST  
PUT  
DELETE

## Study

GET  
POST  
PUT  
DELETE

## Assay

GET  
POST  
PUT  
DELETE

## Report

GET  
POST  
PUT  
DELETE

## Authorise

GET  
POST  
PUT  
DELETE

## Dataset

GET  
POST  
PUT  
DELETE

## AppDomain

GET  
POST  
PUT  
DELETE

## Validation

GET  
POST  
PUT  
DELETE

## Feature

GET  
POST  
PUT  
DELETE

## Compound

GET  
POST  
PUT  
DELETE

## Model

GET  
POST  
PUT  
DELETE

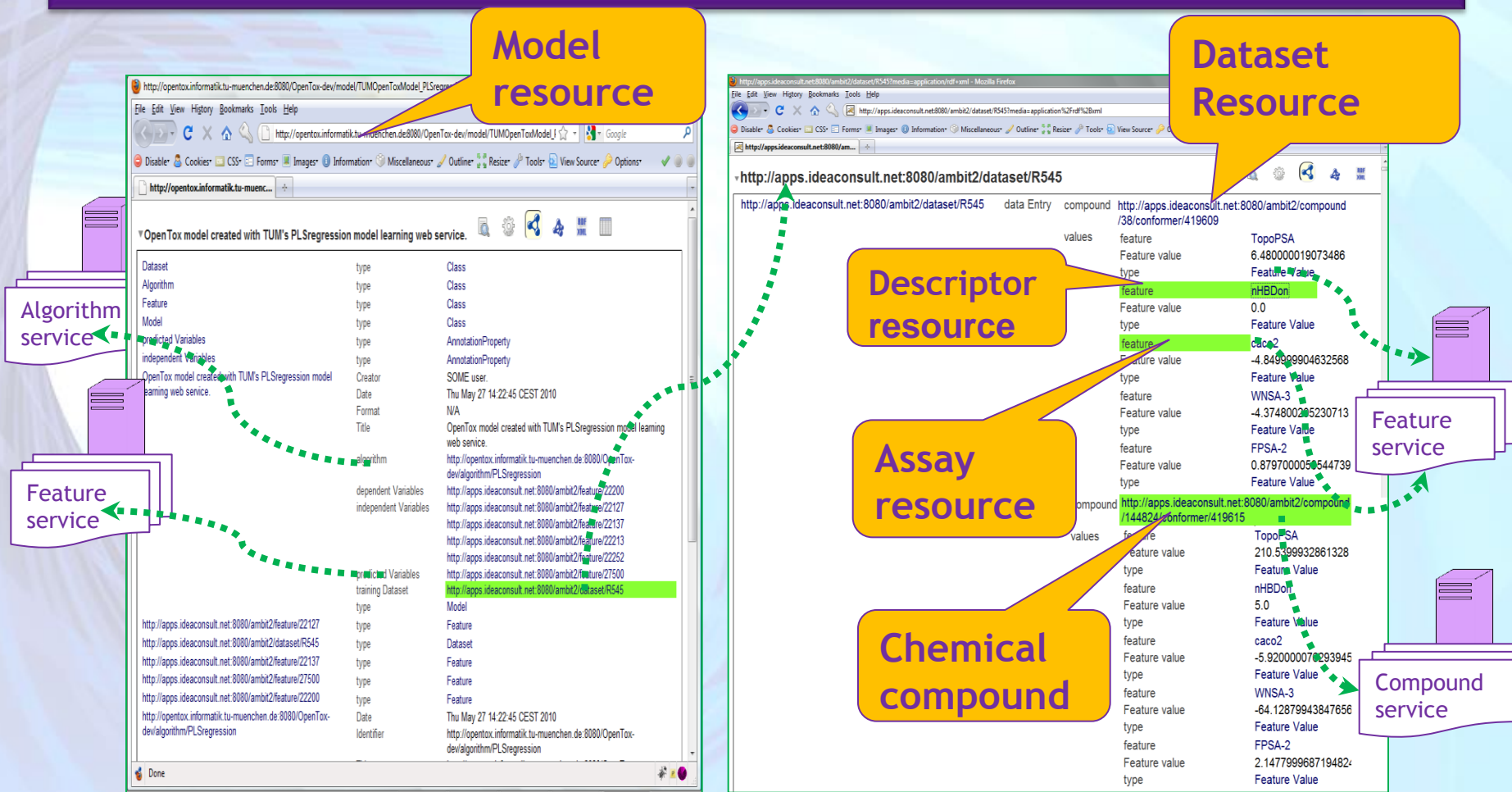
## Algorithm

GET  
POST  
PUT  
DELETE

## Ontology

GET  
POST  
PUT  
DELETE

# Linked resources: Compound, Algorithm, Model, Dataset, Features



# Linked resources: Compound, Algorithm, Model, Dataset, Features

Dataset Resource

Descriptor resource

Assay resource

Chemical compound

data Entry	compound	values
http://apps.ideaconsult.net:8080/ambit2/dataset/R545	http://apps.ideaconsult.net:8080/ambit2/compound/38/conformer/419609	feature TopoPSA Feature value 6.48000019073486 type Feature Value feature nHBDdon Feature value 0.0 type Feature Value feature caco2 Feature value 8.849999904632568 type Feature Value feature WNSA-3 Feature value -374800205230713 type Feature Value feature FPPA-2 Feature value 0.8797000050544739 type Feature Value
http://apps.ideaconsult.net:8080/ambit2/dataset/R545	http://apps.ideaconsult.net:8080/ambit2/compound/144824/conformer/419615	feature TopoPSA Feature value 210.5399938861328 type Feature Value feature nHBDdon Feature value 5.0 type Feature Value feature caco2 Feature value -5.920000076293945 type Feature Value feature WNSA-3 Feature value -64.12879943847856 type Feature Value feature FPPA-2 Feature value 2.147799968719482 type Feature Value

Blue Obelisk algorithms ontology

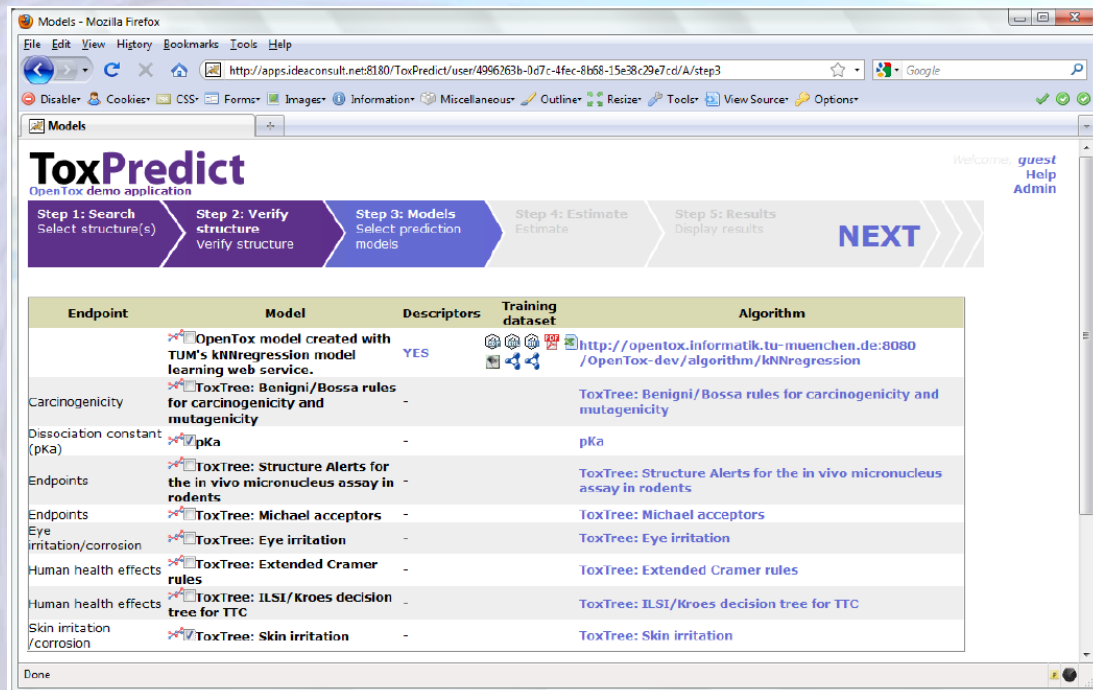
Name of the algorithm	type	Class
	type	Class
Numeric Feature	type	Class
	subClassOf	
Source	type	ObjectProperty
Units	type	DatatypeProperty
nHBDdon	sameAs	http://www.blueobelisk.org/ontologies/cheminformatics-algorithms/#hBondDonors
	Title	nHBDdon
	Source	http://apps.ideaconsult.net:8080/ambit2/algorithm/org.openscience.cdk.qsar.descriptors.molecular.HBondDonorCountDescr
	Units	
	type	Numeric Feature

Regression  
Classification  
Chemistry  
Descriptors, etc

OpenTox algorithm types ontology

Toxicology related ontologies

# Prototyping demonstrated ...



**ToxPredict**  
OpenTox demo application

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

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

**NEXT**

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

Done

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

# First AXLR8 Meeting ...



The screenshot shows the ToxPredict web application interface in a Mozilla Firefox browser window. The URL is <http://apps.ideaconsult.net:8180/ToxPredict/user/4996263b-0d7c-4fec-8b68-15e38c29e7cd/A/step3>. The interface includes a navigation bar with three steps: Step 1: Search (Select structure(s)), Step 2: Verify structure (Verify structure), and Step 3: Models (Select prediction models). Below the navigation bar is a table with columns for Endpoint, Model, and Descriptors.

Endpoint	Model	Descriptors
	OpenTox model created with TUM's kNNregression model learning web service.	YES
Carcinogenicity	ToxTree: Benigni/Bossa rules for carcinogenicity and mutagenicity	-
Dissociation constant (pKa)	pKa	-
Endpoints	ToxTree: Structure Alerts for the in vivo micronucleus assay in rodents	-
Endpoints	ToxTree: Michael acceptors	-
Eye irritation/corrosion	ToxTree: Eye irritation	-
Human health effects	ToxTree: Extended Cramer rules	-
Human health effects	ToxTree: ILSI/Kroes decision tree for TTC	-
Skin irritation/corrosion	ToxTree: Skin irritation	-

Overlaid on the right side of the screenshot is a map of Europe with five green circular markers placed at various locations: two in the north (Germany/Poland area), one in the east (Russia/Ukraine area), one in the south (Italy/Greece area), and one in the southwest (Spain/Portugal area).

*Simple building of applications methods and*

*Distributed applications, integrating wide range of data, models, prediction methods*

# Spring 2010 ...

The image shows a composite of three windows. On the left is the ToxPredict web application interface, which includes a navigation bar with three steps: 'Step 1: Search', 'Step 2: Verify structure', and 'Step 3: Models'. Below this is a table listing various endpoints and their corresponding models and descriptors. In the center is a map of Europe with three green circles highlighting specific locations. On the right is a Taverna workflow diagram, a complex flowchart showing the integration of various services like 'ask\_username', 'calculate\_descriptors', 'learn\_model', and 'apply\_model\_to\_testset'.

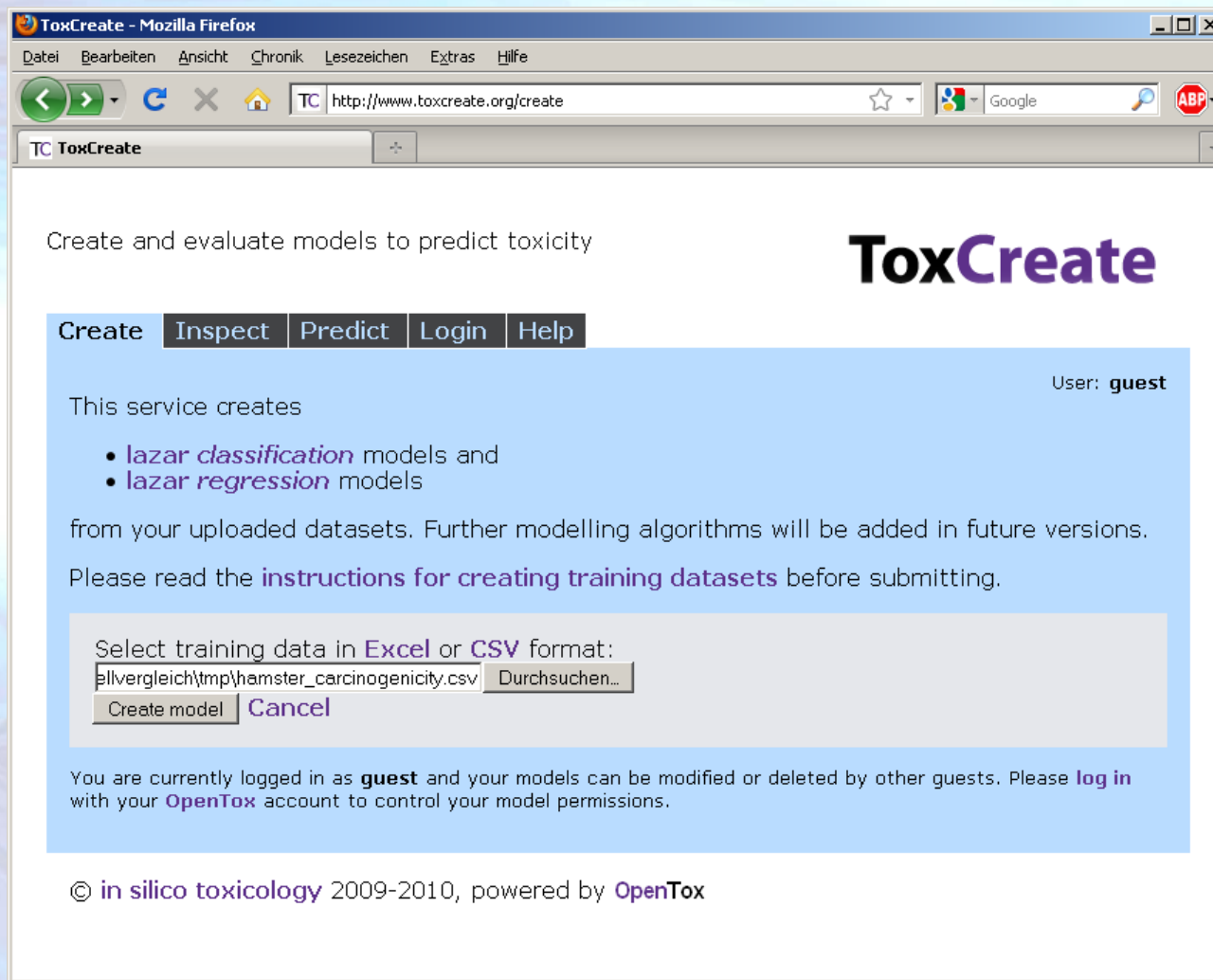
Endpoint	Model	Descriptors
	OpenTox model created with TUM's kNN regression model learning web service.	YES
Carcinogenicity	ToxTree: Benigni/Bossa rules for carcinogenicity and mutagenicity	-
Dissociation constant (pKa)	pKa	-
Endpoints	ToxTree: Structure Alerts for the in vivo micronucleus assay in rodents	-
Endpoints	ToxTree: Michael acceptors	-
Eye irritation/corrosion	ToxTree: Eye irritation	-
Human health effects	ToxTree: Extended Cramer rules	-
Human health effects	ToxTree: ILSI/Kroes decision tree for TTC	-
Skin irritation/corrosion	ToxTree: Skin irritation	-

Simple building of applications methods and

Distributed of wide range of methods

Integration into workflow systems for computational biology

# ToxCreate - (Q)SAR Model Building application



The screenshot shows a Mozilla Firefox browser window with the address bar displaying <http://www.toxcreate.org/create>. The page title is "ToxCreate". The main content area features the heading "Create and evaluate models to predict toxicity" and the "ToxCreate" logo. A navigation menu includes "Create", "Inspect", "Predict", "Login", and "Help". The user is identified as "User: guest". The main text states: "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. A note at the bottom of the form area says: "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." The footer of the page reads: "© [in silico toxicology](#) 2009-2010, powered by [OpenTox](#)".

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

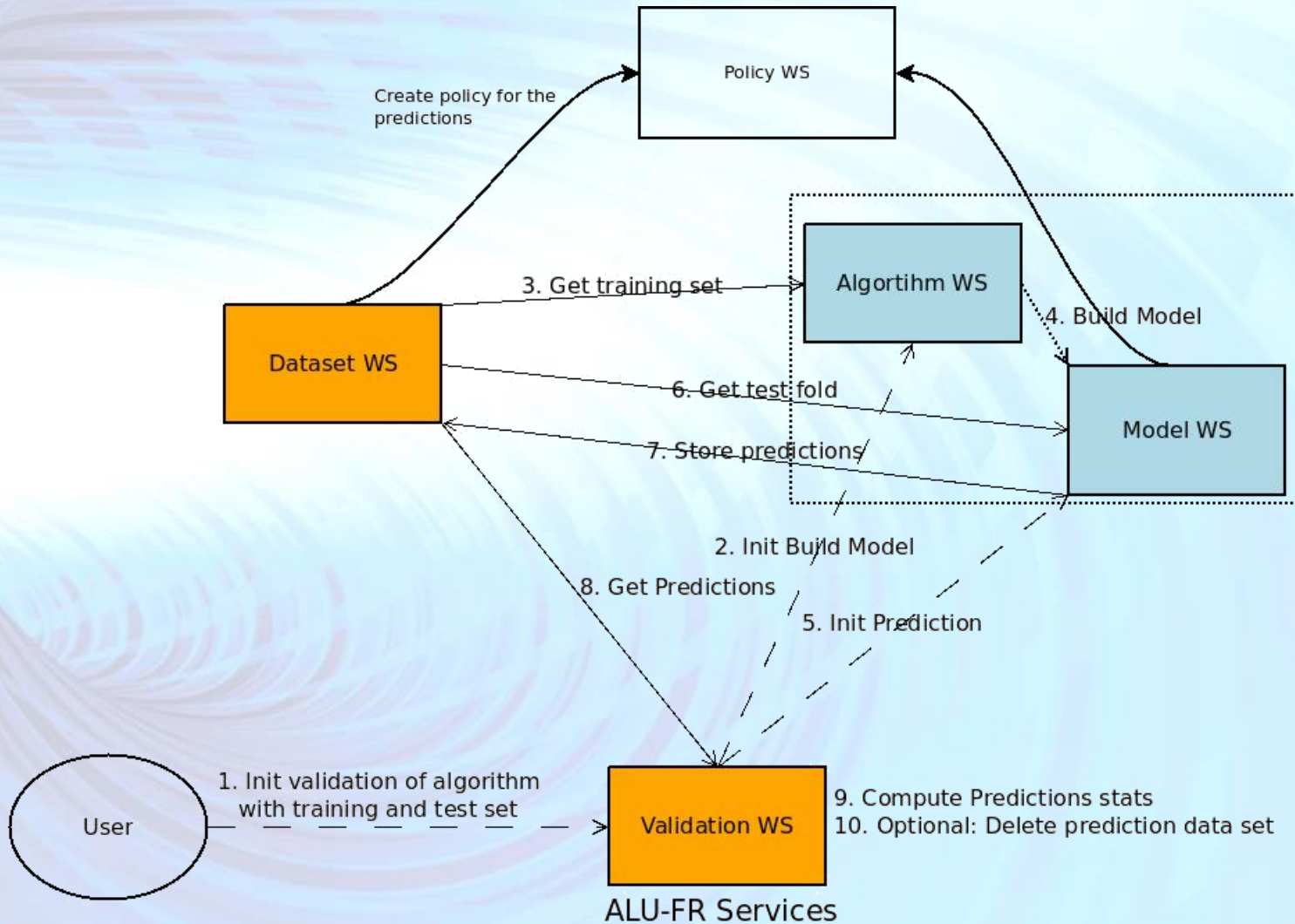
Confusion Matrix:

		Measured	
		active	inactive
Predicted	active	32	5
	inactive	7	25

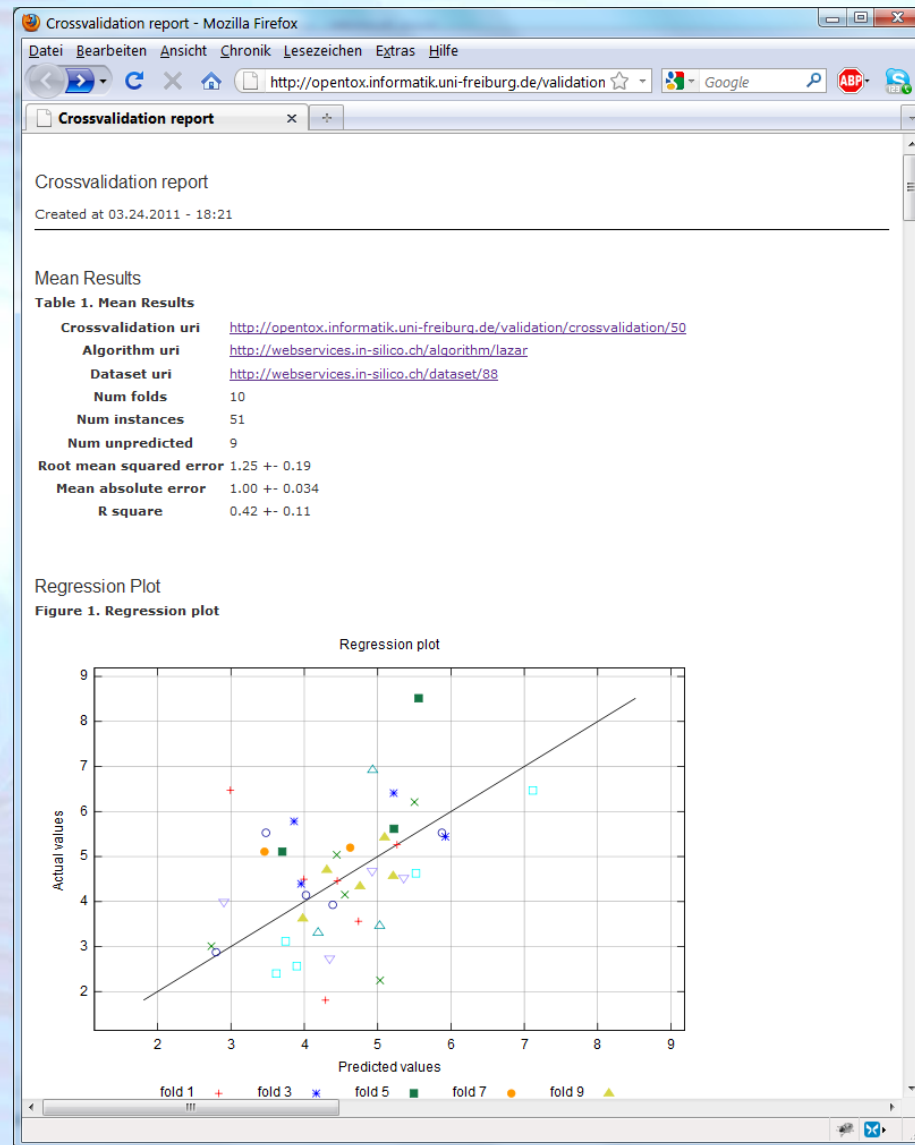
© in silico toxicology 2009-2010, powered by **OpenTox**

	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

ToxCreate - Mozilla Firefox

TC http://www.toxcreate.org/lazar#lazar\_algorithm

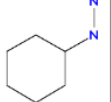
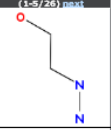
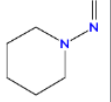
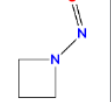
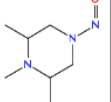
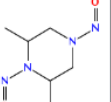
TC ToxCreate phenylhydrazine (CHEBI:27924)

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

Create Inspect **Predict** Login Help

User: **guest**

New prediction

Hamster Carcinogenicity	Prediction	Confidence	Supporting information
 <chem>Nc1ccccc1NN</chem>	active	0.108	Names and synonyms Significant fragments
Neighbors (1-5726) next	Measured activity	Similarity	Supporting information
 <chem>CCN=NN</chem>	inactive	0.715	Names and synonyms Significant fragments
 <chem>C1CCCCC1NN=O</chem>	inactive	0.5	Names and synonyms Significant fragments
 <chem>C1CCN1</chem>	inactive	0.5	Names and synonyms Significant fragments
 <chem>C1=NC=NC=N1</chem>	inactive	0.5	Names and synonyms Significant fragments
 <chem>C1=NN=CN1</chem>	inactive	0.5	Names and synonyms Significant fragments

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# QPRF Reporting (Qedit)

The screenshot displays the Qedit software interface for reporting QPRF results. 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 the "Applicability Domain" section.

**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: <http://ambit.uni-plovdiv.bg:8080/ambit2/compound/5100/conformer/5100>

Smiles: [Ca+2].CCCC1(C(=O)NC(=NC1=O)[O-])C2=CCCCC2.CCC3(C(=O)NC(=NC3=O)C(=O)O)C4=CC=CC=C4

InChI:

InChI Key:

CAS number:

Chemical Name:

Einecs:

REACH Reg. Date:

Available Conformers (Links):

- <http://ambit.uni-plovdiv.bg:8080/ambit2/compound/5100/conformer/5100>
- <http://ambit.uni-plovdiv.bg:8080/ambit2/compound/5100/conformer/105301>
- <http://ambit.uni-plovdiv.bg:8080/ambit2/compound/5100/conformer/181274>

Buttons:

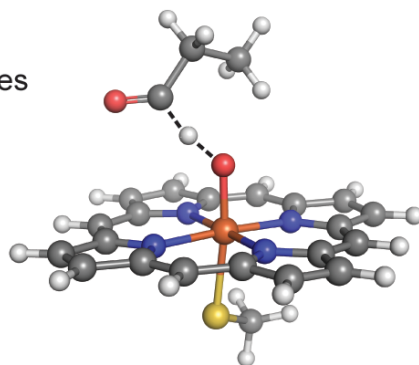
Application by Pantelis Sopasakis (NTUA)

# SMARTCyp Service for Predicting Metabolites

## Atom Reactivity Library

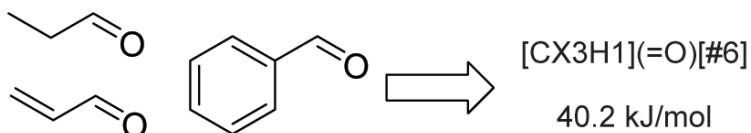
### A. Calculate Quantum Chemical Reference Energies

Calculate transition state energies using density functional theory



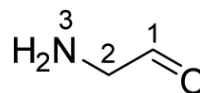
### B. Define SMARTS Rules

Group calculations by fragments and calculate average energies



## SMARTCyp

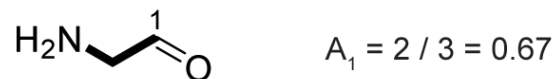
### 1. Assign Energies By SMARTS matching



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

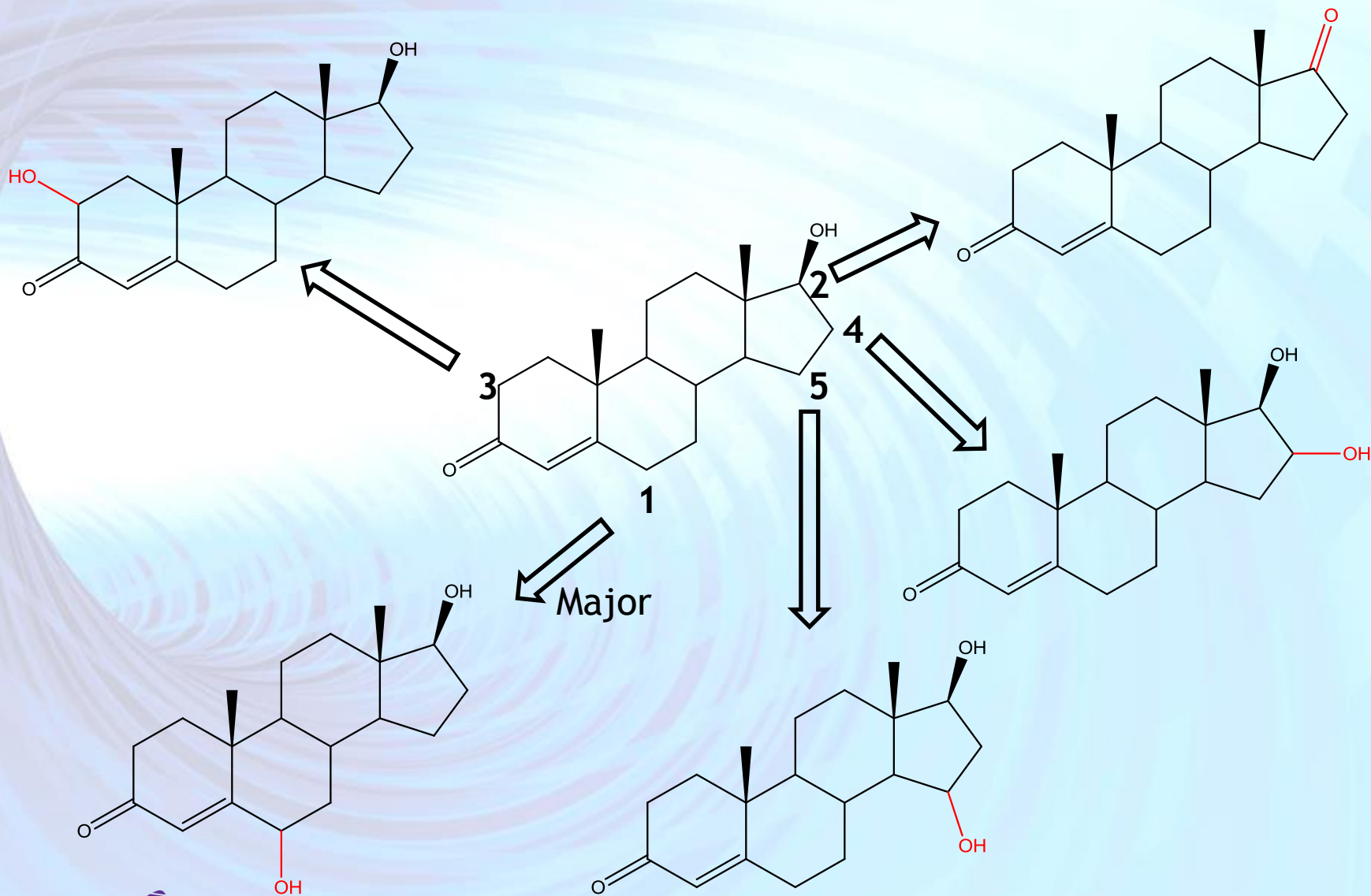
Atom 3 - Rank 3



SMARTCyp - developed by Patrik Rydberg, University of Copenhagen

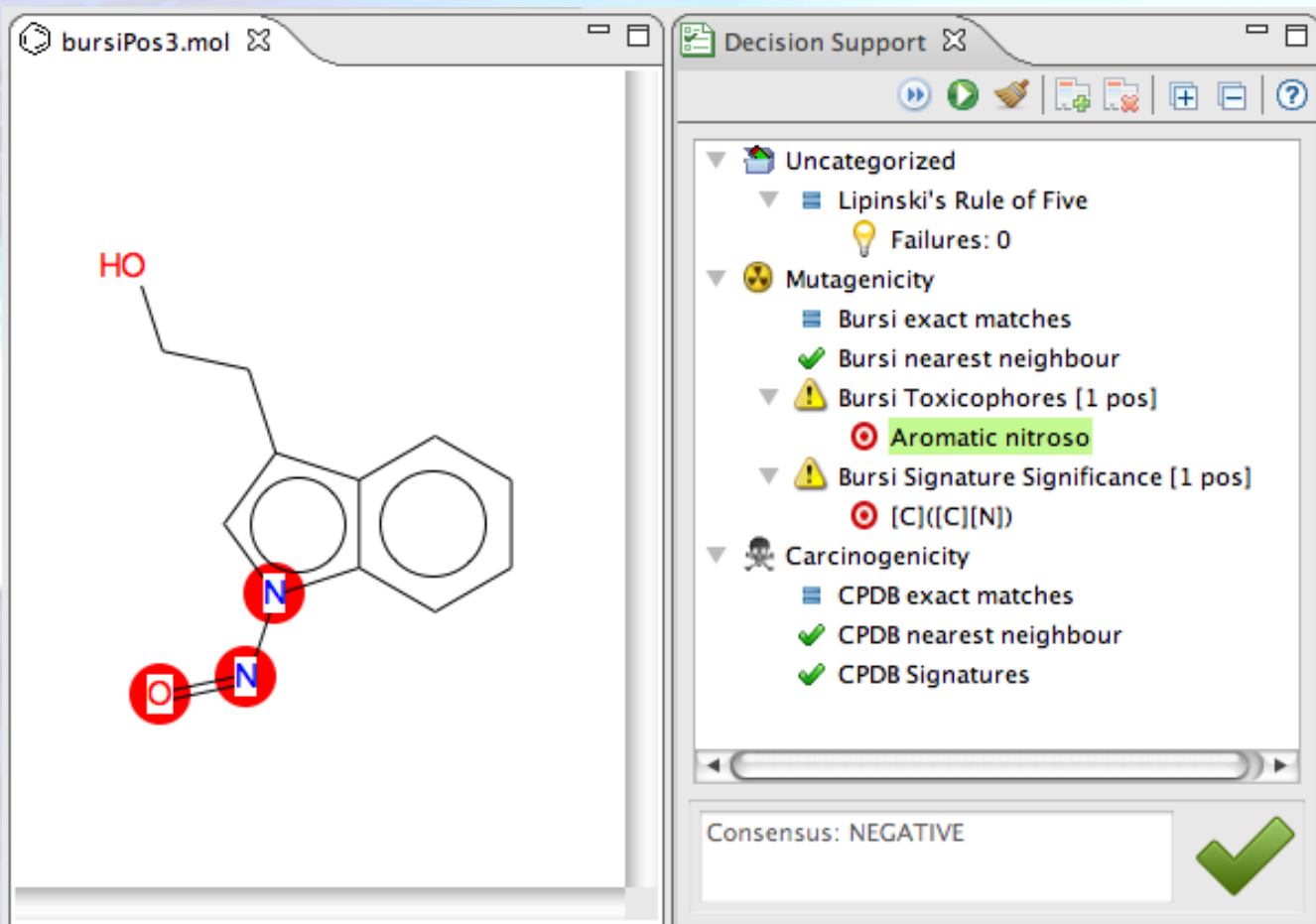
[www.farma.ku.dk/index.php/SMARTCyp/7990/0/](http://www.farma.ku.dk/index.php/SMARTCyp/7990/0/)

# SmartCYP Prediction of Testosterone Metabolites





# Bioclipse Visualisation Workbench - OpenTox



Collaboration with Ola Spjuth  
and Egon Willighagen



Bioclipse-OpenTox Integration - See Application example in Chapter in [Open Source Software in Life Science Research: Practical Solutions to Common Challenges in the Pharmaceutical Industry and Beyond](#) (Woodhead Publishing Series in Biomedicine) edited by Lee Harland and Mark Forster (30 Oct 2012)

# Bioclipse Visualisation Workbench - OpenTox

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 'H' is visible on the left side of the structure. The structure is connected to a decision support panel on the right. The panel lists various alerts and their significance, including AHR Signature Alerts, Carcinogenicity, CPDB Signature Alerts, Mutagenicity, and Ames Signature Alerts. The consensus result is shown as 'NEGATIVE' with a green checkmark.

Decision Support

- 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

Collaboration with Ola Spjuth  
and Egon Willighagen



Bioclipse-OpenTox Integration - See Application example in Chapter in [Open Source Software in Life Science Research: Practical Solutions to Common Challenges in the Pharmaceutical Industry and Beyond](#) (Woodhead Publishing Series in Biomedicine) edited by Lee Harland and Mark Forster (30 Oct 2012)

# Bioclipse Visualisation Workbench - OpenTox

The screenshot displays the Bioclipse software interface. The main window shows a chemical structure of a steroid-like molecule with an epoxide ring highlighted in red. The word "Changed" is written in purple above the structure. To the right, a "Decision Support" panel lists various alerts and metrics:

- 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

Below the structure, a "Properties" table is visible:

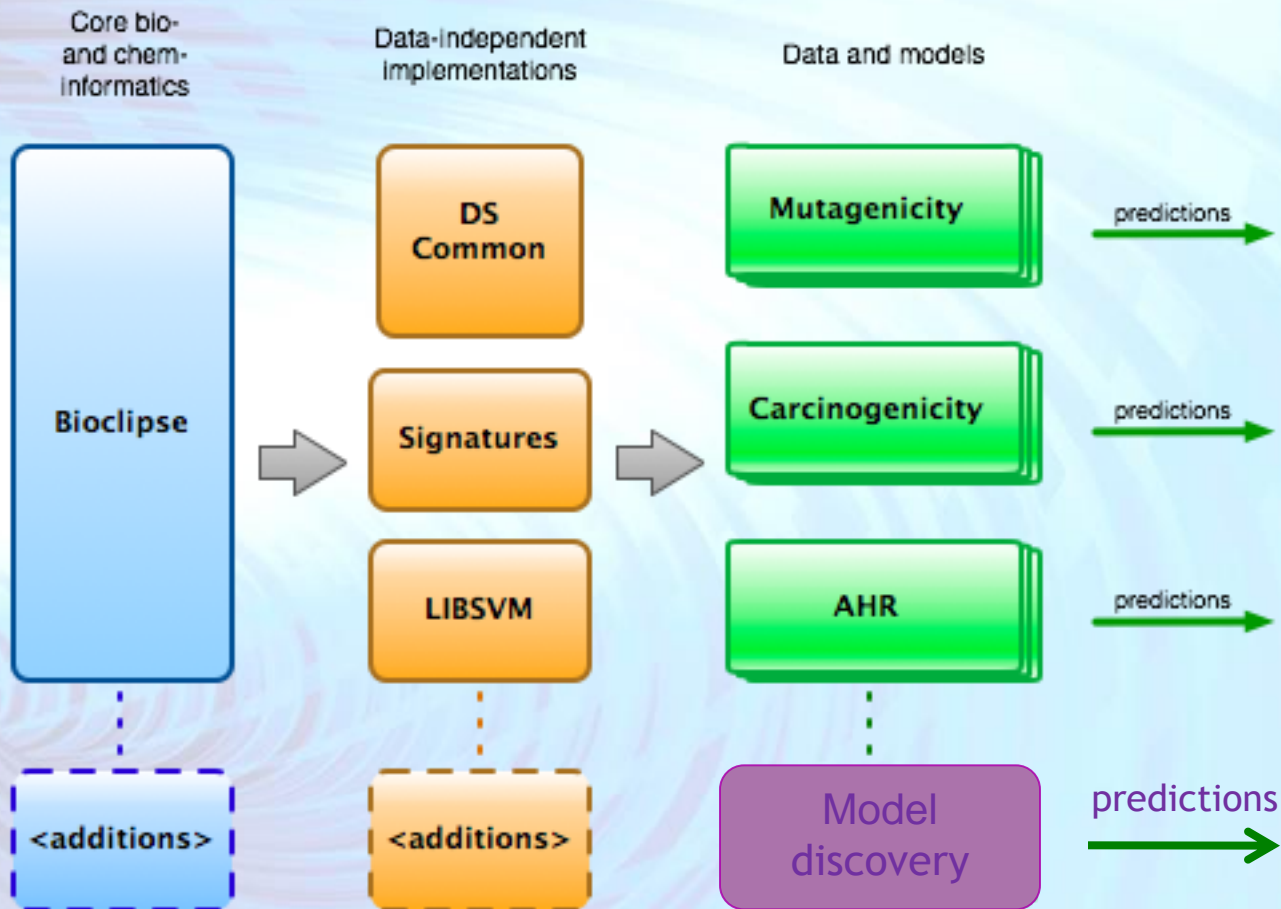
Property	Value
General	
Classification	POSITIVE
Matching atoms	22, 21, 23
Name	Epoxide
Test	Ames Structural Alerts

Collaboration with Ola Spjuth  
and Egon Willighagen



Bioclipse-OpenTox Integration - See Application example in Chapter in [Open Source Software in Life Science Research: Practical Solutions to Common Challenges in the Pharmaceutical Industry and Beyond](#) (Woodhead Publishing Series in Biomedicine) edited by Lee Harland and Mark Forster (30 Oct 2012)

# Bioclipse - OpenTox Interoperation



OpenTox

# Visualisation of chemical feature-based categories

OpenTox

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



### Abstract

Scientific researchers in the field of chemoinformatics often deal with large chemical datasets. Therefore, the need for visualizing the structure of these datasets, and multi-dimensional similarity, is increasingly becoming essential. This tool provides essential information allowing easy and understandable access to a large dataset. The different clustering approaches employed in this tool are based on the underlying scientific knowledge of a part of a given dataset for further analysis.

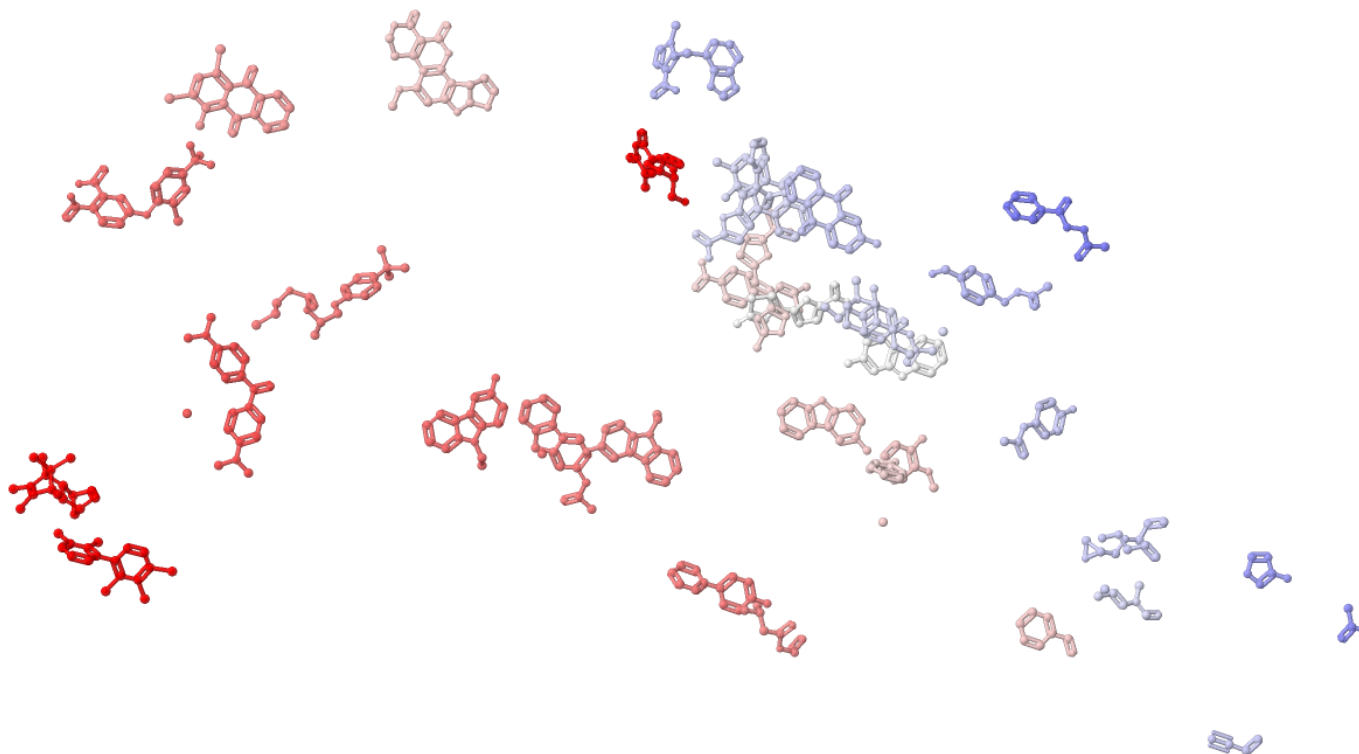
### Build 3D Structure Extract Features

- 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 descriptors with CDK

### Cluster Compound

- Compounds in the dataset are assigned 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 features
    - Compounds are assigned to cluster there exists a common subgraph
- 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://www.open-tox.org>

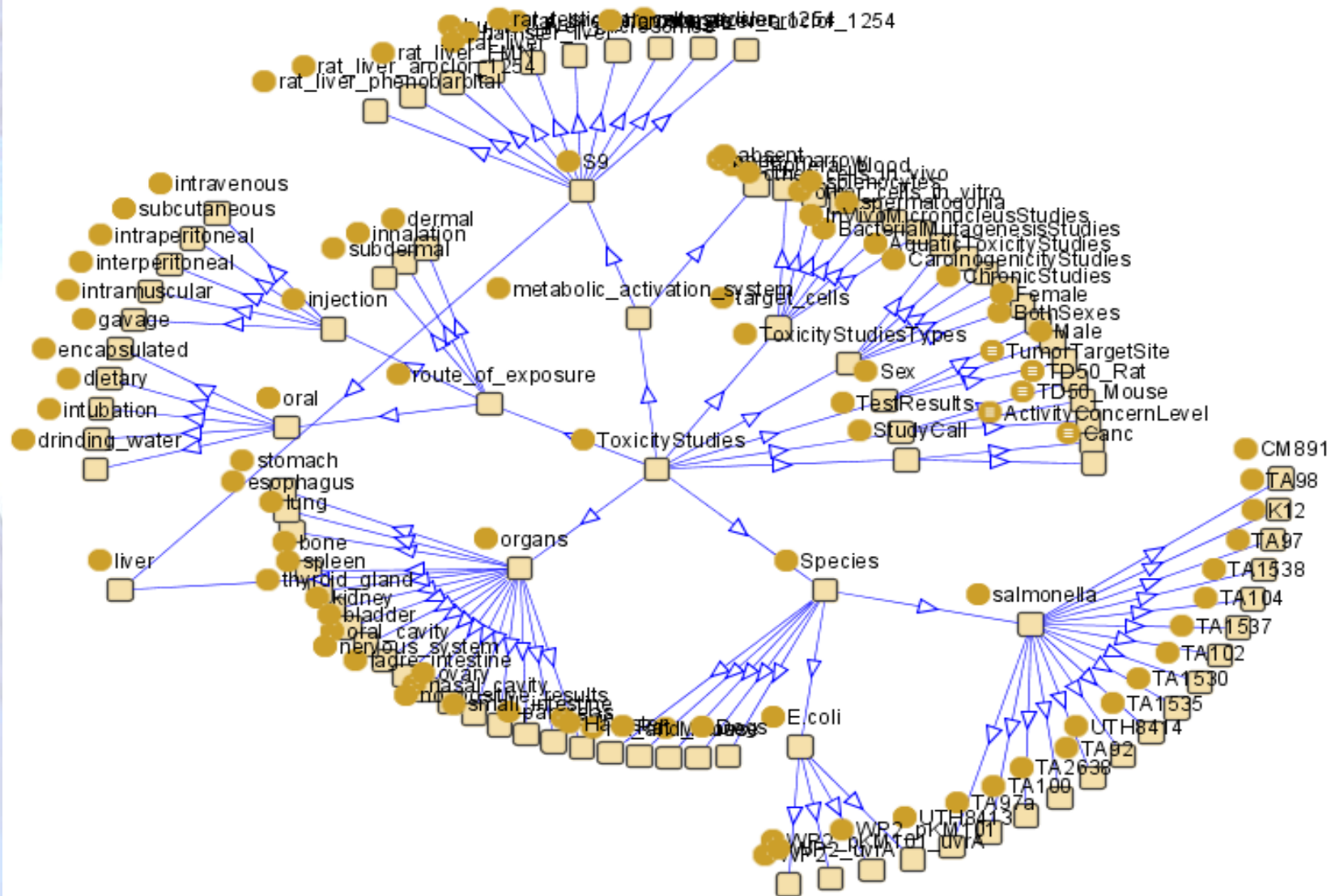


# Definition of Ontology

In computer science and information science, an ontology formally represents **knowledge** as a set of **concepts** within a domain, and the **relationships** between those concepts. It can be used to **model** a domain and support **reasoning** about concepts.

In theory, an ontology is a "**formal, explicit specification** of a shared conceptualisation". An ontology provides a **shared vocabulary**, which can be used to model a domain, that is, the type of objects and/or concepts that exist, and their **properties** and relations.

# Toxicological Ontology: graphical representation



# Toxicology Ontology Developments and Roadmap



- See perspectives and roadmap published in A Toxicology Ontology Roadmap **ALTEX 29(2), 129- 137** and Toxicology Ontology Perspectives **139 - 156** (2012)
- Available online in Open Access mode from [www.altex.ch](http://www.altex.ch)
- Barry Hardy (Douglas Connect and OpenTox), Gordana Apic (Cambridge Cell Networks), Philip Carthew (Unilever), Dominic Clark (EMBL-EBI), David Cook (AstraZeneca), Ian Dix (AstraZeneca & Pistoia Alliance), Sylvia Escher (Fraunhofer Institute for Toxicology & Experimental Medicine), Janna Hastings (EMBL-EBI), David J. Heard (Novartis), Nina Jeliaskova (Ideaconsult), Philip Judson (Lhasa Ltd.), Sherri Matis-Mitchell (AstraZeneca), Dragana Mitic (Cambridge Cell Networks), Glenn Myatt (Leadscope), Imran Shah (US EPA), Ola Spjuth (University of Uppsala), Olga Tcheremenskaia (Istituto Superiore di Sanità), Luca Toldo (Merck KGaA), David Watson (Lhasa Ltd.), Andrew White (Unilever), Chihae Yang (Altamira)

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

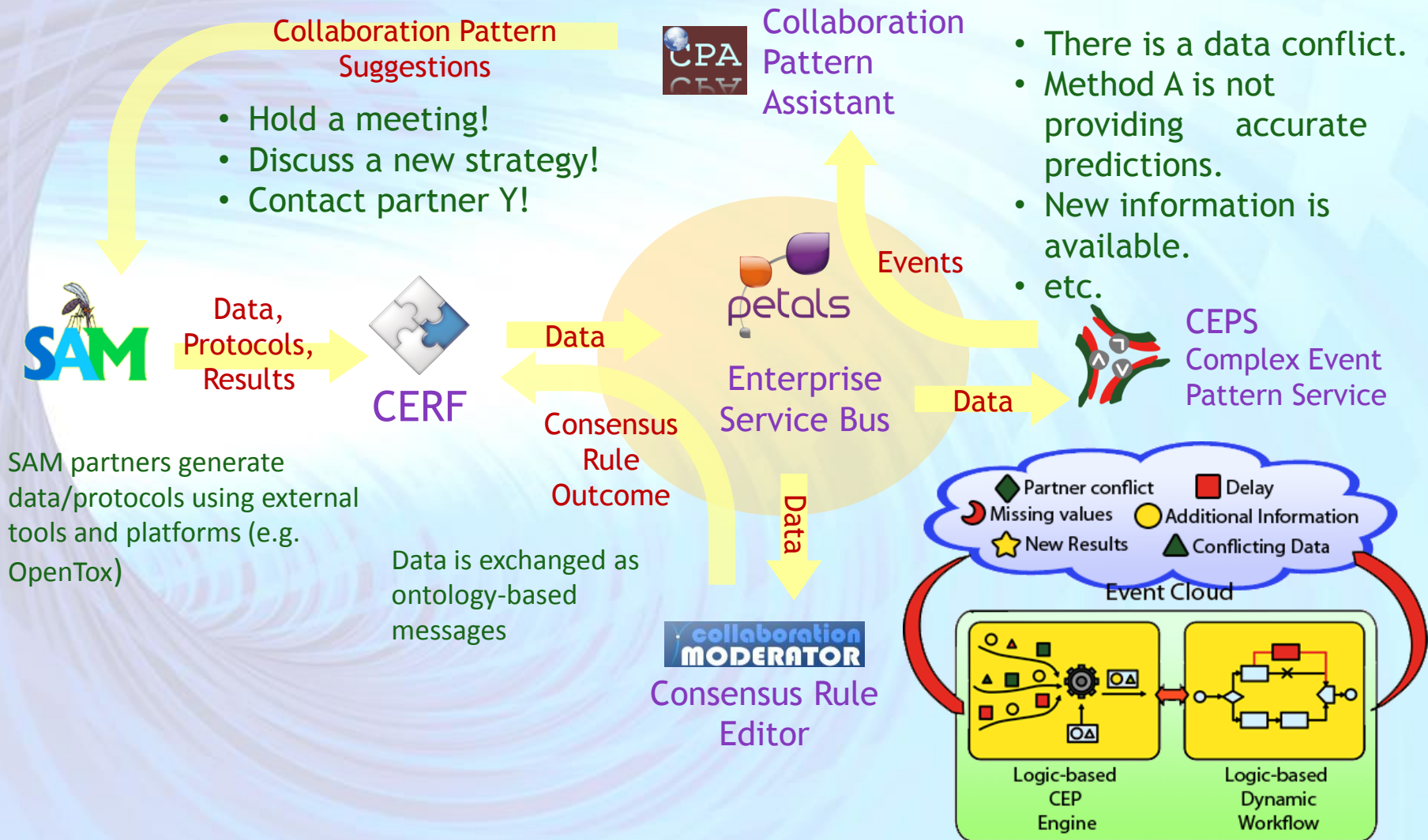


# Weight of Evidence

“An evidence based approach involves an **assessment** of the relative values/weights of different pieces of the available **information** that have been retrieved and gathered in previous steps. To this end, a value needs to be assigned to each piece of information. These weights/values can be assigned either in an *objective* way by using a formalised procedure or by using expert judgement. The weight given to the available evidence will be influenced by factors such as the **quality of the data**, **consistency of results**, nature and severity of effects, relevance of the information for the given regulatory endpoint.

One definition for weight of evidence is: ‘the process of considering the **strengths and weaknesses** of various pieces of information in reaching and supporting a **conclusion** concerning a **property** of the substance.’ Within the REACH legislation, the so-called weight of evidence approach is a component of the **decision-making** procedure on substance properties and thus an important part of the chemical safety assessment.»

# Event-driven Collaboration Architecture



SAM partners generate data/protocols using external tools and platforms (e.g. OpenTox)

Data is exchanged as ontology-based messages

- There is a data conflict.
- Method A is not providing accurate predictions.
- New information is available.
- etc.

[Hardy and Affentranger, Drug Discovery Today.](#)

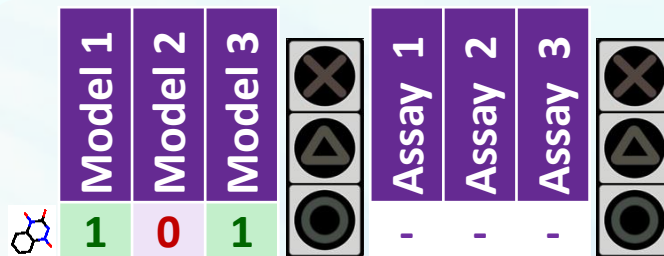
[2013 Jul;18\(13-14\):681-6.](#)

# Event Driven Weight of Evidence

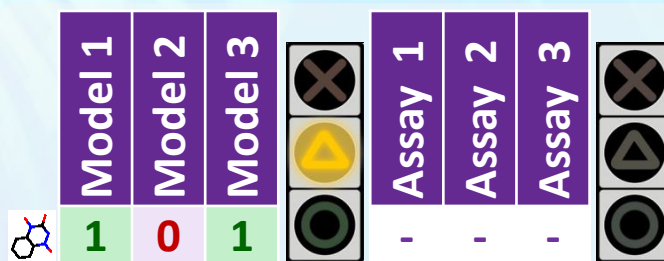
collaboration  
**MODERATOR**

Consensus Rule  
Editor

## Recommendation Rules:



**Synergy**



**OpenTox**



# 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	Phase	VS	Dock	Dock 2	Binding Prediction Stoplight	QSAR ADME	QSPP 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			1	1				-10.47	-10.8												
UC0000864			1	1				-10.2	-10.9												
UC0000884			1	1				-9.1400003	-10.6												
UC0000885			1	1				-9.1400003	-10.5												
UC0000886			1	1				-9.41	-10.6												
UC0000921			1	1				-10.91	-9.1000004												
UC0001349			1	1				-9.9799995	-11.2												
UC0001350			1	1				-9.96	-11.2												
UC0001500			1	1				-9.3299999	-9.3999996												
UC0001501			1	1				-9.5699997	-9.6000004												
UC0001623			1	1				-9.4899998	-9.1000004												
UC0001624			1	1				-9.4899998	-9.1000004												
UC0001699			1	1				-12.2	-10.9												
UC0001700			1	1				-9.9899998	-9.8000002												
UC0001702			1	1				-13.37	-9.6000004												
UC0001703			1	1				-10.61	-10.7												
UC0001743			1	1				-9.29	-9.1000004												
UC0001775			1	1				-9.7700005	-9.1000004												
UC0001875			1	1				-9.84	-9.2												
UC0001987			1	1				-9.7700005	-9.1999998												
UC0002838			1	1				-9.1999998	-9.8999996												
UC0002854			1	1				-10.09	-10.0												
UC0003266			1	1				-9.4799995	-9.8000002												
UC0003454			1	1				-9.1899996	-10.0												
UC0003835			1	1				-9.1000004	-9.8000002												
UC0003867			1	1				-10.25	-9.3999996												
UC0003923			1	1				-9.7200003	-9.8000002												
UC0003941			1	1				-10.52	-9.3000002												
UC0003973			1	1				-9.3100004	-9.1999998												

Previous Next Results per page: 100

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 ?

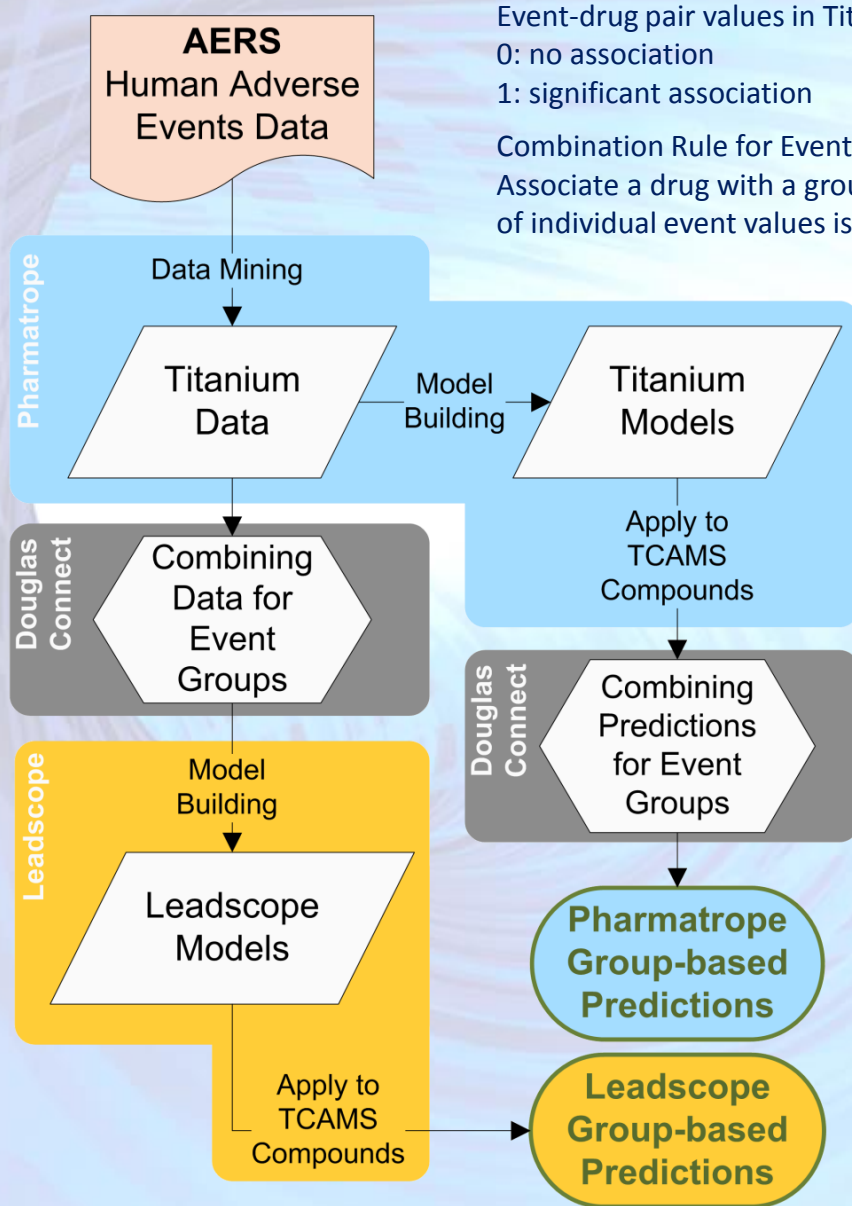
[Hardy and Affentranger, Drug Discovery Today. 2013 Jul;18\(13-14\):681-6.](#)

# Need for Ontology

A Weight of Evidence requires

**A common open public toxicology ontology supporting the review process, the capturing of the results and their synthesis into applications supporting decision-making and judgement.**

# Human Adverse Events Data



Event-drug pair values in Titanium Data:

- 0: no association
- 1: significant association

Combination Rule for Event Groups:  
Associate a drug with a group if the sum of individual event values is non-zero

Event-drug pair values in Titanium Predictions:

- 0 : no association (0)
- 0.35-0.4 : non-significant association (0)
- > 0.4 : significant association (1)

Combination Rule for Event Groups:  
Associate a drug with a group if the sum of individual event values is larger of equal to 0.4.

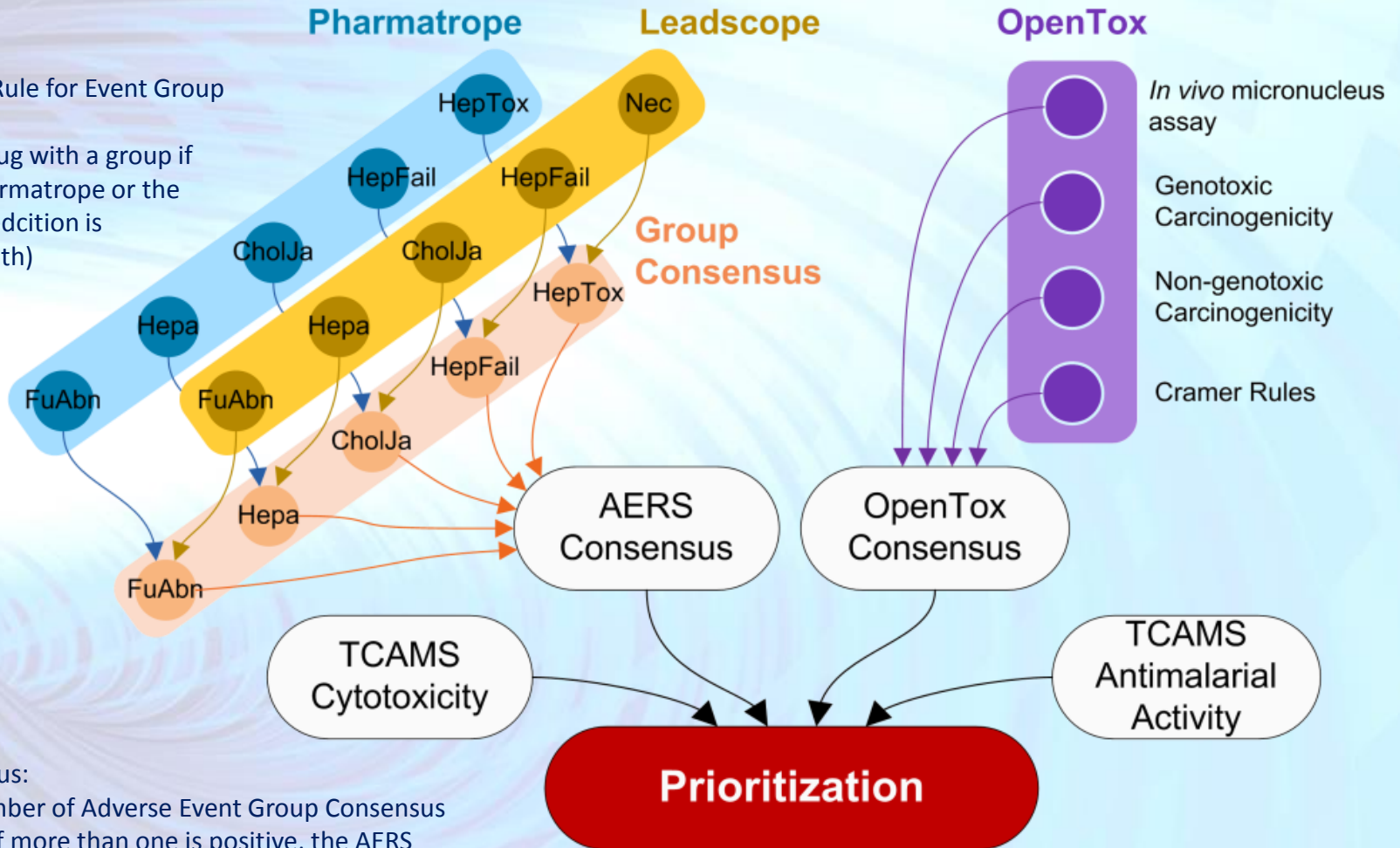
## Adverse Event Groups

## Group Name

Hepatic function abnormal Liver disorder	<b>FuAbn</b>
Hepatic necrosis	<b>Nec</b>
Cytolytic hepatitis Hepatitis Hepatitis acute Hepatitis toxic	<b>Hepa</b>
Cholestasis Jaundice Hepatitis cholestatic jaundice cholestatic Yellow skin	<b>CholJa</b>
Hepatic failure Hepatitis fulminant Acute hepatic failure Hepatorenal failure	<b>HepFail</b>
Hepatotoxicity Hepatomegaly Hyperbilirubinaemia Hepatosplenomegaly	<b>HepTox</b>

# Combining Predictions and Experimental Data

Combination Rule for Event Group Predictions:  
Associate a drug with a group if either the Pharmatrope or the Leadscope prediction is positive (or both)



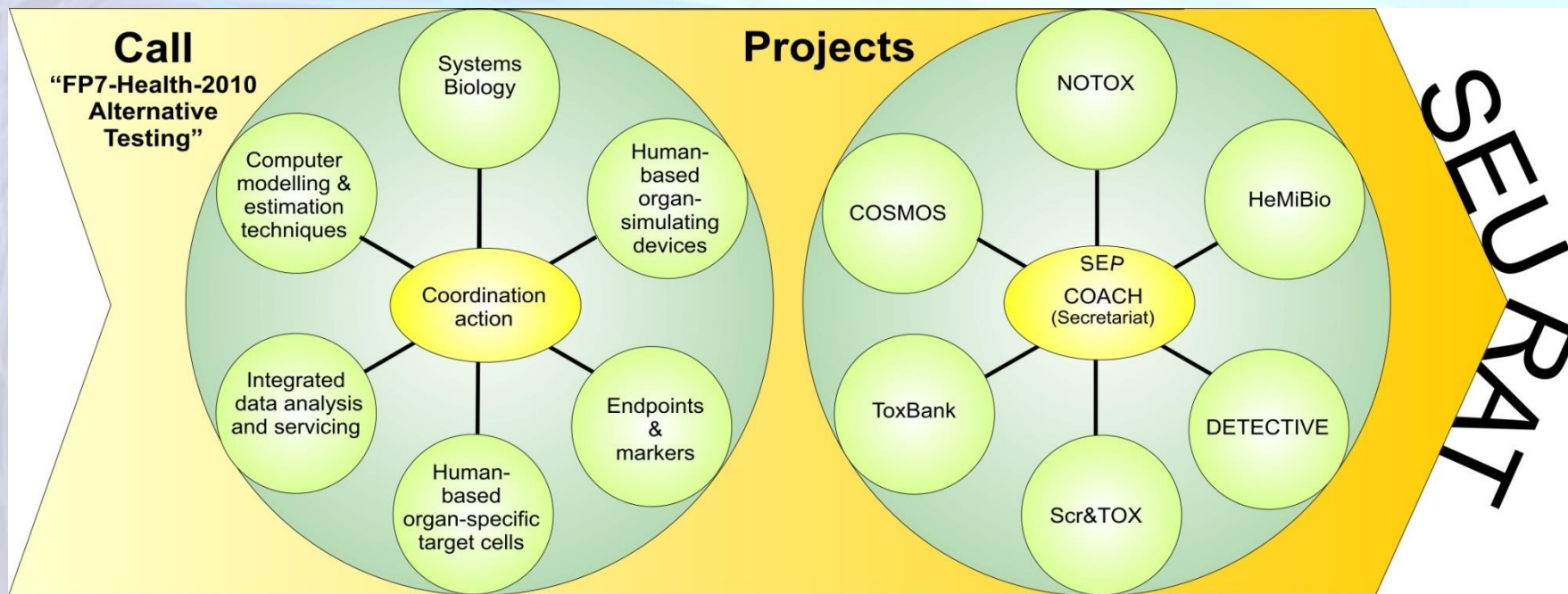
AERS Consensus:  
Count the number of Adverse Event Group Consensus associations. If more than one is positive, the AERS Consensus is positive.

OpenTox Consensus:  
Negative if both carcinogenicity and the micronucleus assay predictions are negative, OR if the Cramer Rule classification is Class I. Positive otherwise.

TCAMS Cytotoxicity:  
Positive if > 30% growth inhibition at 10  $\mu$ M.

TCAMS Antimalarial Activity:  
Positive if > 80% growth inhibition of *P. Falciparum* DD2 at 2  $\mu$ M.

# The Building Blocks of SEURAT-1

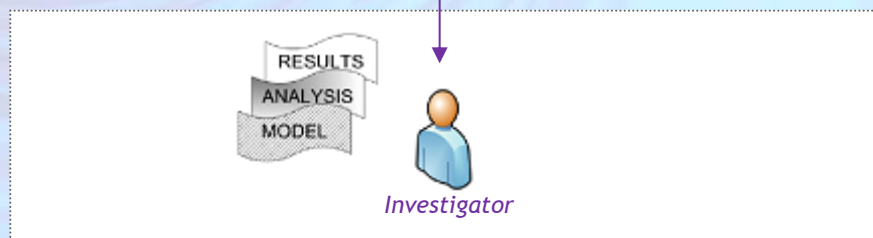
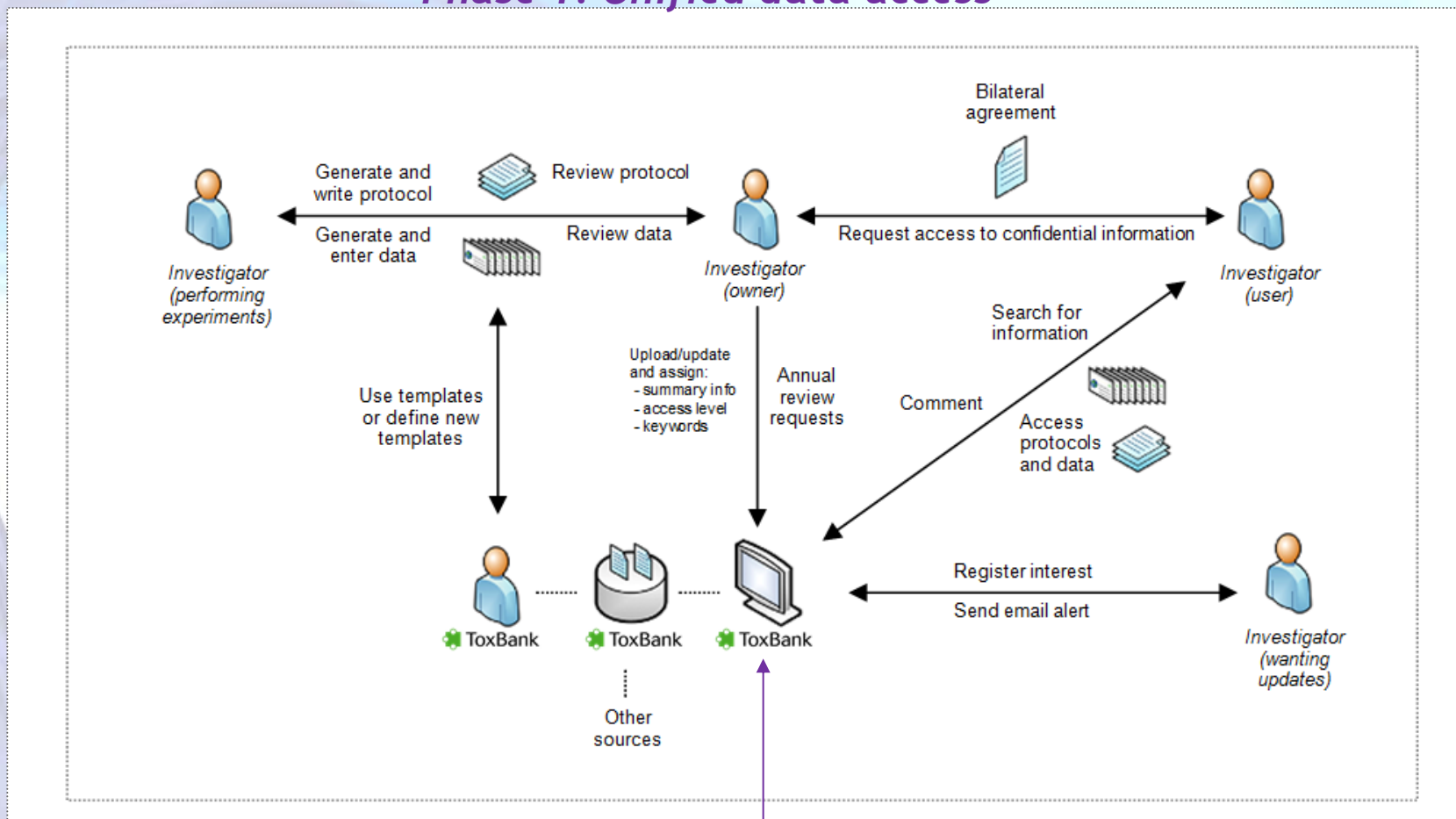


~ 70 research groups from European Universities,  
Public Research Institutes and Companies  
(more than 30% SMEs)



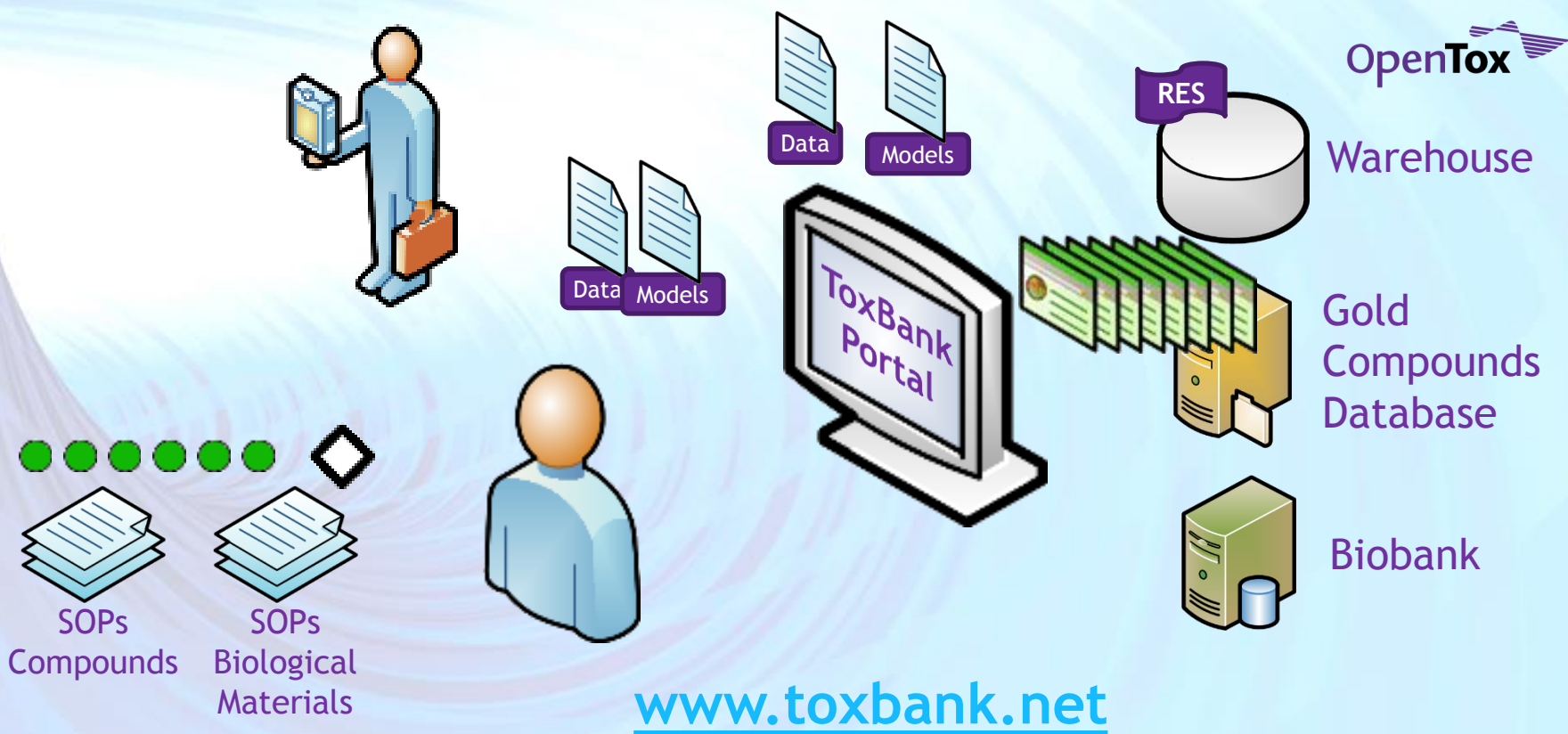
# Outline of the ToxBank Data Warehouse

## Phase 1: Unified data access

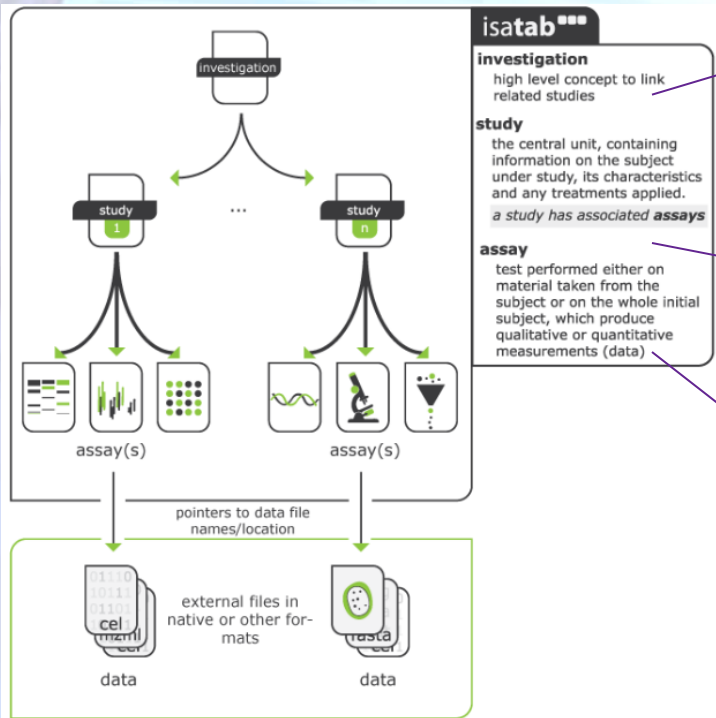


# ToxBank Infrastructure System Vision

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



# ISATab archives are created for each investigation



Investigation ID	Investigation Title	Investigation Description	Investigation Submitter	Investigation Public Release Date	Investigation Public Release Status	Investigation Public Release Title	Investigation Public Release Description	Investigation Public Release Status	Investigation Public Release Term Accession Number	Investigation Public Release Term Accession Number
1	Investigation 1	Investigation 1 Description	Investigator 1	2010-01-01	Public	Investigation 1 Title	Investigation 1 Description	Investigation 1 Status	Investigation 1 Term Accession Number	Investigation 1 Term Accession Number
2	Investigation 2	Investigation 2 Description	Investigator 2	2010-01-01	Public	Investigation 2 Title	Investigation 2 Description	Investigation 2 Status	Investigation 2 Term Accession Number	Investigation 2 Term Accession Number

Overall investigation design and information (i... files)

Study ID	Study Title	Study Description	Assay ID	Assay Name	Assay Description	Assay Status	Assay Term Accession Number
1	Study 1	Study 1 Description	1	Assay 1	Assay 1 Description	Public	Assay 1 Term Accession Number
1	Study 1	Study 1 Description	2	Assay 2	Assay 2 Description	Public	Assay 2 Term Accession Number

Study description (s... files)

Assay ID	Assay Name	Assay Description	Test Results
1	Assay 1	Assay 1 Description	Test Results 1
2	Assay 2	Assay 2 Description	Test Results 2

Test results (a... files) with links to data table or native file (e.g. CEL files)

# ToxBank integrates systems biology concepts into toxicological assessment

Pekka Kohonen,<sup>[a]</sup> Emilio Benfenati,<sup>[b]</sup> David Bower,<sup>[c]</sup> Rebecca Ceder,<sup>[a]</sup> Michael Crump,<sup>[c]</sup> Kevin Cross,<sup>[c]</sup> Roland C. Grafström,<sup>[a]</sup> Lyn Healy,<sup>[d]</sup> Christoph Helma,<sup>[e]</sup> Nina Jeliaskova,<sup>[f]</sup> Vedrin Jeliaskov,<sup>[f]</sup> Silvia Maggioni,<sup>[b]</sup> Scott Miller,<sup>[c]</sup> Glenn Myatt,<sup>[c]</sup> Michael Rautenberg,<sup>[e]</sup> Glyn Stacey,<sup>[d]</sup> Egon Willighagen,<sup>[a]</sup> Jeff Wiseman,<sup>[g]</sup> and Barry Hardy<sup>[h]</sup>; <sup>[a]</sup>Karolinska Institutet, Institute for Environmental Medicine, Molecular Toxicology, Stockholm, Sweden; <sup>[b]</sup> Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; <sup>[c]</sup> Leadscope, Columbus, USA; <sup>[d]</sup> National Institute for Biological Standards and Control, Potters Bar, UK; <sup>[e]</sup> In silico toxicology, Basel, Switzerland; <sup>[f]</sup> Ideacon, Sofia, Bulgaria; <sup>[g]</sup> Pharmatrop, Wayne, USA; <sup>[h]</sup> Douglas Connect, Zeiningen, Switzerland.

## Conclusions - great potential to contribute to

- ❖ toxicity evaluation based on **Mode-of-Action**
- ❖ decreased need for animal experiments

## Systems toxicology - principles

Understanding the **toxicological interactions** in **biological systems** under **compound challenges**

## Based on developments in high-throughput biology

- ❖ 'Omics profiling: *gene expression, proteins, metabolites and others*
- ❖ *cell-based screening*: High-Throughput and High-Content analyses

## Risk assessment carried out primarily using

- ❖ *in vitro*
- ❖ *In silico* methods

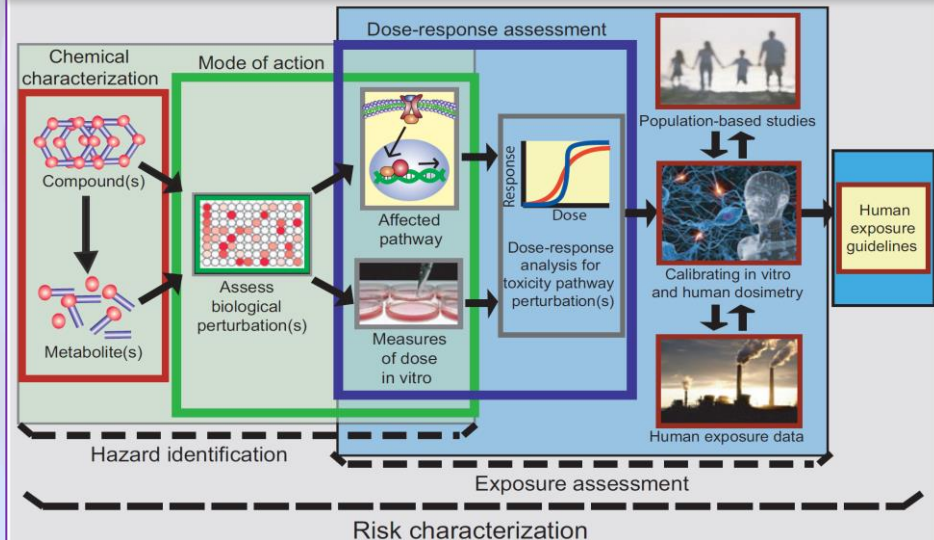


Figure 1. Multiple tools will be step by step, implemented into an innovative toxicity testing strategy based on mode-of-action.

Kohonen P. et al. The ToxBank Data Warehouse: Supporting the Replacement of In Vivo Repeated Dose Systemic Toxicity Testing. *Molecular Informatics*. 17 JAN 2013, DOI: 10.1002/minf.201200114.

## Clustering by Gene Ontology

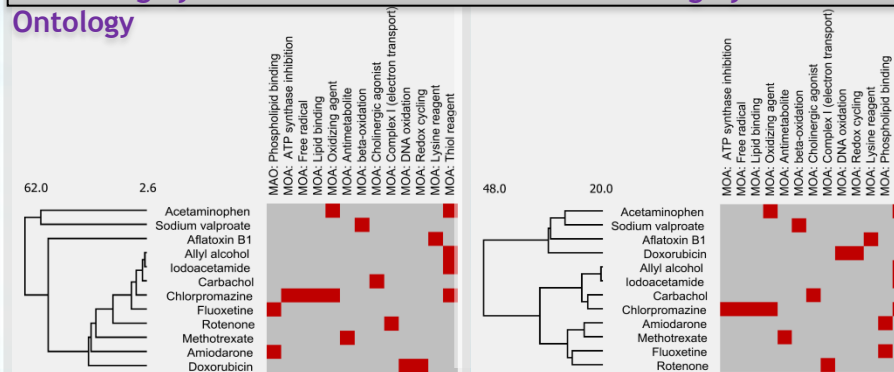


Figure 2. Clustering of ToxBank Gold Compounds by biological similarity using chemical-genome links from Comparative Toxicogenomics Database (CTD). Compounds with similar Mode-of-Action cluster together.

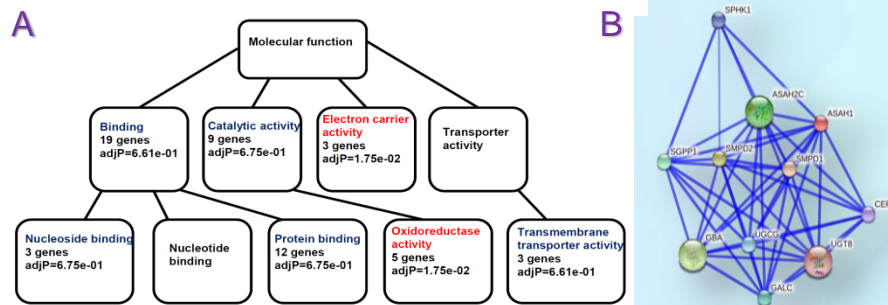
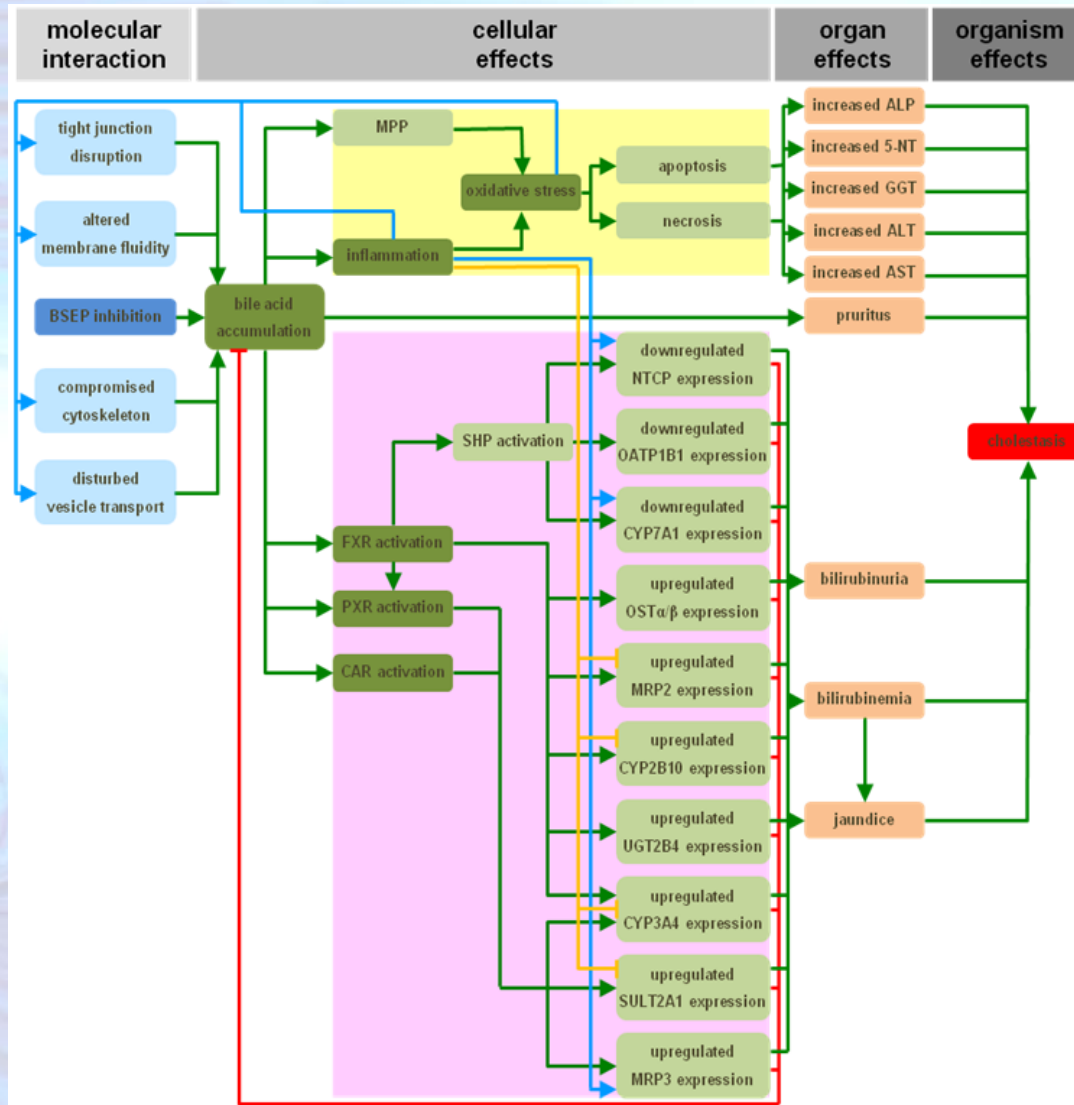


Figure 3. A) Enriched gene ontology (GO) categories of genes associated with the oxidizing agent mode-of-action (MOA) B) Protein-protein association network around the AsaH1 protein. Associated with phospholipid binding MOA.


## ToxBank builds databases and data management solutions to aid in systems toxicology-based risk assessment

# Adverse outcome pathway (AOP) : drug-induced cholestasis



Vinken M., Landesmann B., Goumenou M., Vinken S., Shah I., Jaeschke H., Willett C., Whelan M., Rogiers V. (2013) Development of an adverse outcome pathway from drug-mediated bile salt export pump inhibition to cholestatic liver injury. *Archives of Toxicology*: submitted .

# New data may be combined with reviewed community data on reference compounds

 **ToxBank**

Supporting integrated data access and analysis across SEURAT-1

Search

Upload

G.Myatt's Settings

Sign Out

**Published Protocol**

**Protocol Document:**

**Protocol ID:**

**Version:**

**Protocol Title:**

**Abstract:**

Email the owner to request access: [U.Summer school](#)

SEURAT-Protocol-38-1

1

In vitro test for py


Parenteral pharm  
pyrogenic (fever-  
general be define  
pyrogens that alm  
pharmaceuticals  
LPS) from Gram-  
1979b). There are  
contamination: th  
amoebocyte lysat  
detects LPS and  
body temperature  
a sterile solution  
LAL test detects  
the bacterial endo  
that LPS causes  
(haemolymph) of  
& Page 1084)

**Related links**

[Gold compound Wiki \(Acetaminophen\)](#)

[Search PubMed for related terms](#)

[Subscribe for updates to this protocol](#)

 **ToxBank**

- Main page
- Recent changes
- Hepatotoxins
  - Summary Page
  - Acetaminophen
  - Aflatoxin B1
  - Amiodarone
  - Bosentan
  - CCl4
  - Chlorpromazine
  - Dimethoxy-naphthoquinone (DMNQ)
  - Iodoacetamide
  - Methotrexate
  - Rotenone
  - Tamoxifen
  - Valproic Acid
- Cardiotoxins
- Special Substances
- Toolbox

Glennmyatt My talk My preferences My watchlist New messages My contributions

Page Discussion

## Acetaminophen

Acetaminophen

### Executive Summary Information

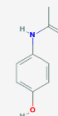
Compound	Acetaminophen (Paracetamol)
Toxicities	Cytotoxicity
Mechanisms	Metabolic oxidation to the quinone imine NAPQI metabolite, which traps cellular thiols, both protein and GSH, by formation of covalent adducts. Studies of quinone imine analogues suggest additional depletion of thiols by redox cycling.
Comments	Acetaminophen is selected based on its chemical mechanism, which is representative of quinones with a high reduction potential.
Feedback Contact	Gold Compound Working Group (GCWG) <a href="#">@</a>


[In Vivo Data](#) [LIINTOP Data](#) [PK-ADME Data](#) [Omics and IC<sub>50</sub> Data](#) [Physical Properties](#)

Recommended Product and Source




In Vivo Data ?	Compound Assessment
Adverse Events ?	High doses can cause acute hepatic necrosis due to production of toxic quinone imine metabolite (NAPQI). From 1998 to 2003, acetaminophen was the leading cause of acute liver failure in the United States, with 48% of acetaminophen-related cases (131 of 275) associated with accidental

### Acetaminophen


CC(=O)Nc1ccc(O)cc1

 **ToxBank**

[wiki.toxbank.net](http://wiki.toxbank.net)



# ToxBank Wiki Reference Information Resource



Page [Discussion](#) [Read](#) [Edit](#) [View history](#)

## Main Page

Main Page

### ToxBank Wiki [\[edit\]](#)

The following wiki pages provide information on compounds and biological materials developed as part of the [SEURAT-1](#) cluster through the ToxBank project. The research leading to these results has received funding from [Cosmetics Europe](#) and the [European Community's Seventh Framework Programme](#) (FP7/2007-2013) under grant agreement n° [267042]. This wiki site reflects only the authors' views. The European Community and Cosmetics Europe are not liable for any use that may be made of the information contained herein.

### Gold compounds wiki pages [\[edit\]](#)

Information on this wiki is based on the research and compound selection tasks performed by the Gold Compound Working Group (GCWG) using a selection criteria outlined by members of the GCWG. Further background information may be available from this working group or under review; selected reviewed materials are made available here.

- [Hepatotoxic Compounds](#)
- [Cardiotoxic Compounds](#)
- [Selection Criteria](#)

Questions, inquiries, comments and feedback regarding the **scientific content** on these pages may be directed to the [Gold Compound Working Group \(GCWG\)](#). The email will automatically be sent to all members on the GCWG group.

Assistance with wiki access or issues with the website in general may be directed to [Micha Rautenberg](#) or [David Bower](#) of the ToxBank project.

### Biological materials wiki pages [\[edit\]](#)

This wiki contains information on cells and reagents relevant to the SEURAT-1 cluster. The following document provides guidance for the banking and supply of human embryonic stem cells:

- [Consensus guidance for banking and supply of human embryonic stem cell lines for research purposes.](#)

Questions, inquiries, comments and feedback regarding the scientific content on these pages may be directed to the [Luam Kidane](#) at the UK Stem Cell Bank.

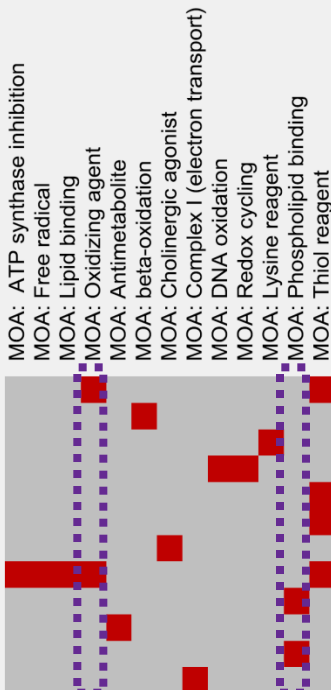
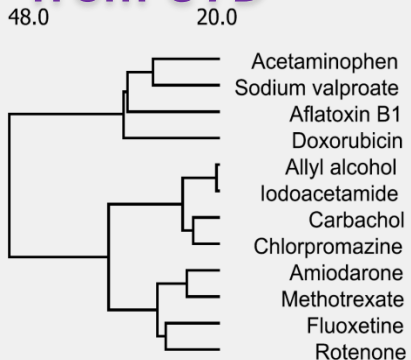
### Recent News [\[edit\]](#)

A report detailing the compound selection strategy was produced as a result of the numerous insightful meetings held at the [Seurat-1 2<sup>nd</sup> Annual Meeting](#) and may be downloaded [here](#).

Main page  
Recent changes

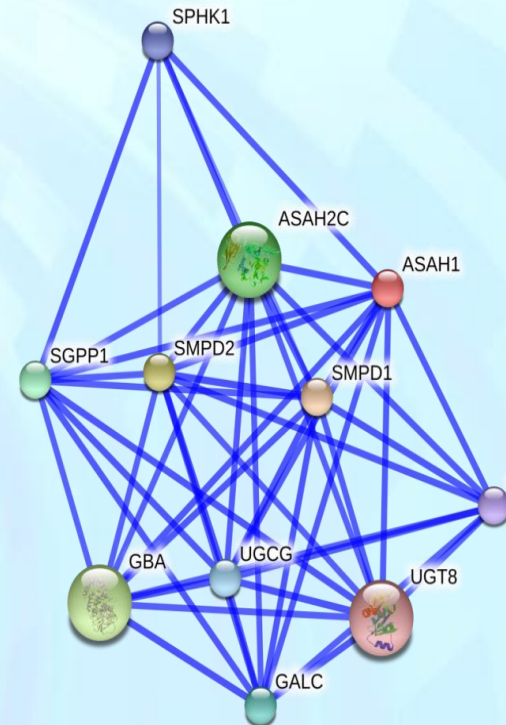
- Hepatotoxins
- Cardiotoxins
- Renal Toxins
- Special Substances
- Undifferentiated Stem Cells
- Reagents (Growth Factors)
- [Reagents \(Antibodies\)](#)
- Reagents (Others)
- Suppliers (Cells)
  - ALSPAC
  - Asterand
  - Biopredic
  - Cellartis
  - Cellular Dynamics
  - DSMZ
  - HPACC
  - ICLC
  - Lonza BioResearch
  - Riken Bioscience

# Clustering by Gene Ontology associations from CTD\*



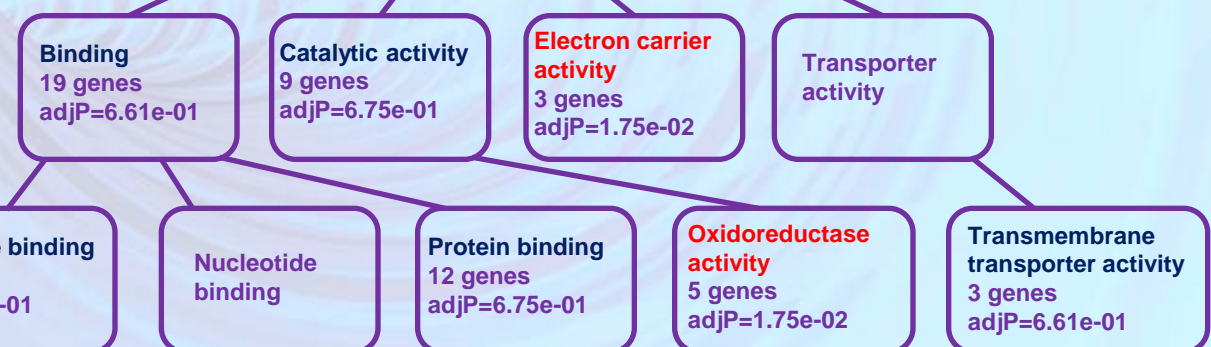
# Public Data Analysis

## Phospholipid Binding



\*CTD = Comparative Toxicogenomics Database  
[www.ctd.org](http://www.ctd.org)

## Oxidative Agent





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## The ToxBank Data Warehouse: Supporting the Replacement of In Vivo Repeated Dose Systemic Toxicity Testing

Pekka Kohonen<sup>1</sup>, Emilio Benfenati<sup>2</sup>, David Bower<sup>3</sup>, Rebecca Ceder<sup>1</sup>, Michael Crump<sup>3</sup>, Kevin Cross<sup>3</sup>, Roland C. Grafström<sup>1</sup>, Lyn Healy<sup>4</sup>, Christoph Helma<sup>5</sup>, Nina Jeliaskova<sup>6</sup>, Vedrin Jeliaskov<sup>6</sup>, Silvia Maggioni<sup>2</sup>, Scott Miller<sup>3</sup>, Glenn Myatt<sup>3</sup>, Michael Rautenberg<sup>5</sup>, Glyn Stacey<sup>4</sup>, Egon Willighagen<sup>1</sup>, Jeff Wiseman<sup>7</sup>, Barry Hardy<sup>8,\*</sup>

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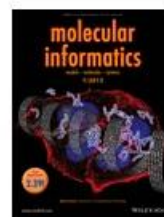
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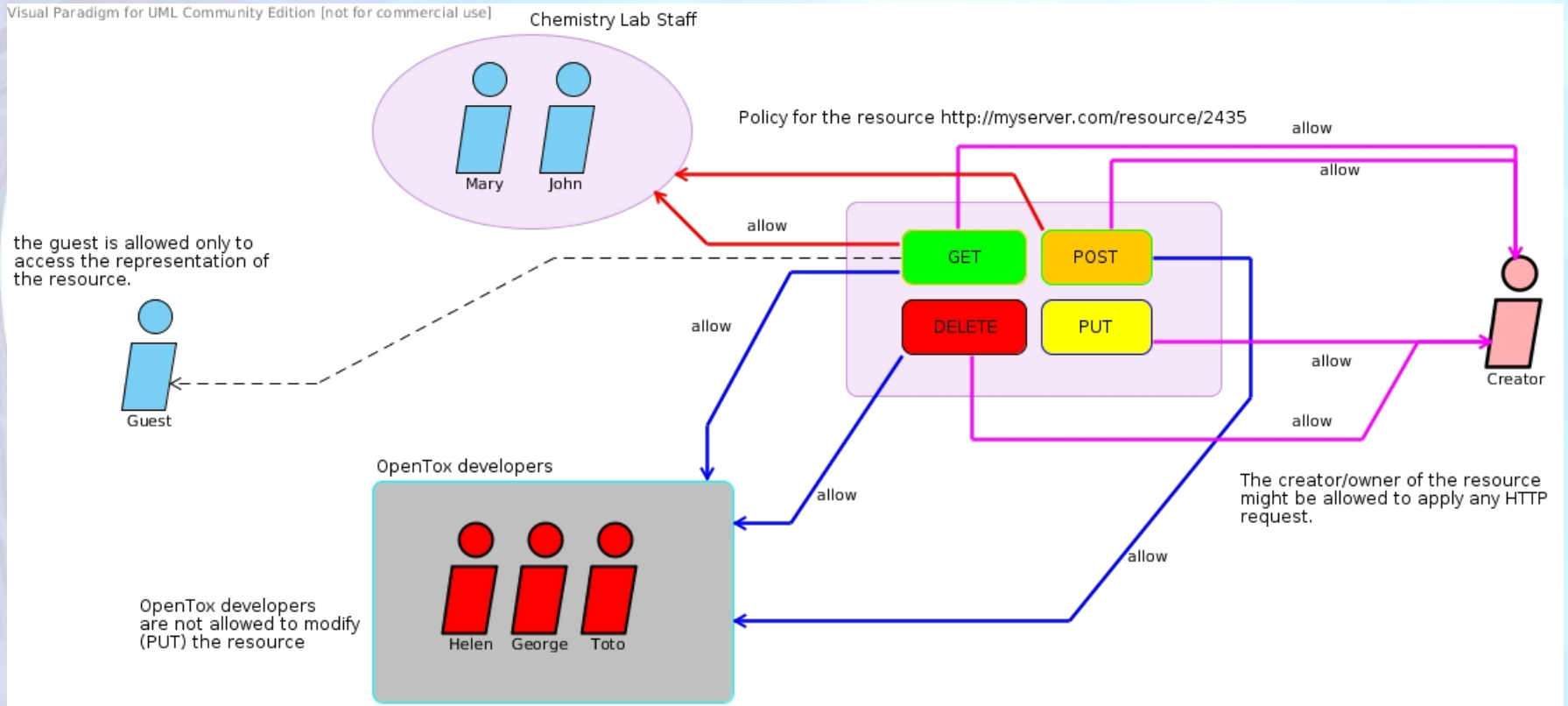
### Molecular Informatics

Special Issue: Advances in Computational Toxicology

**Volume 32, Issue 1, pages 47-63, January 2013**

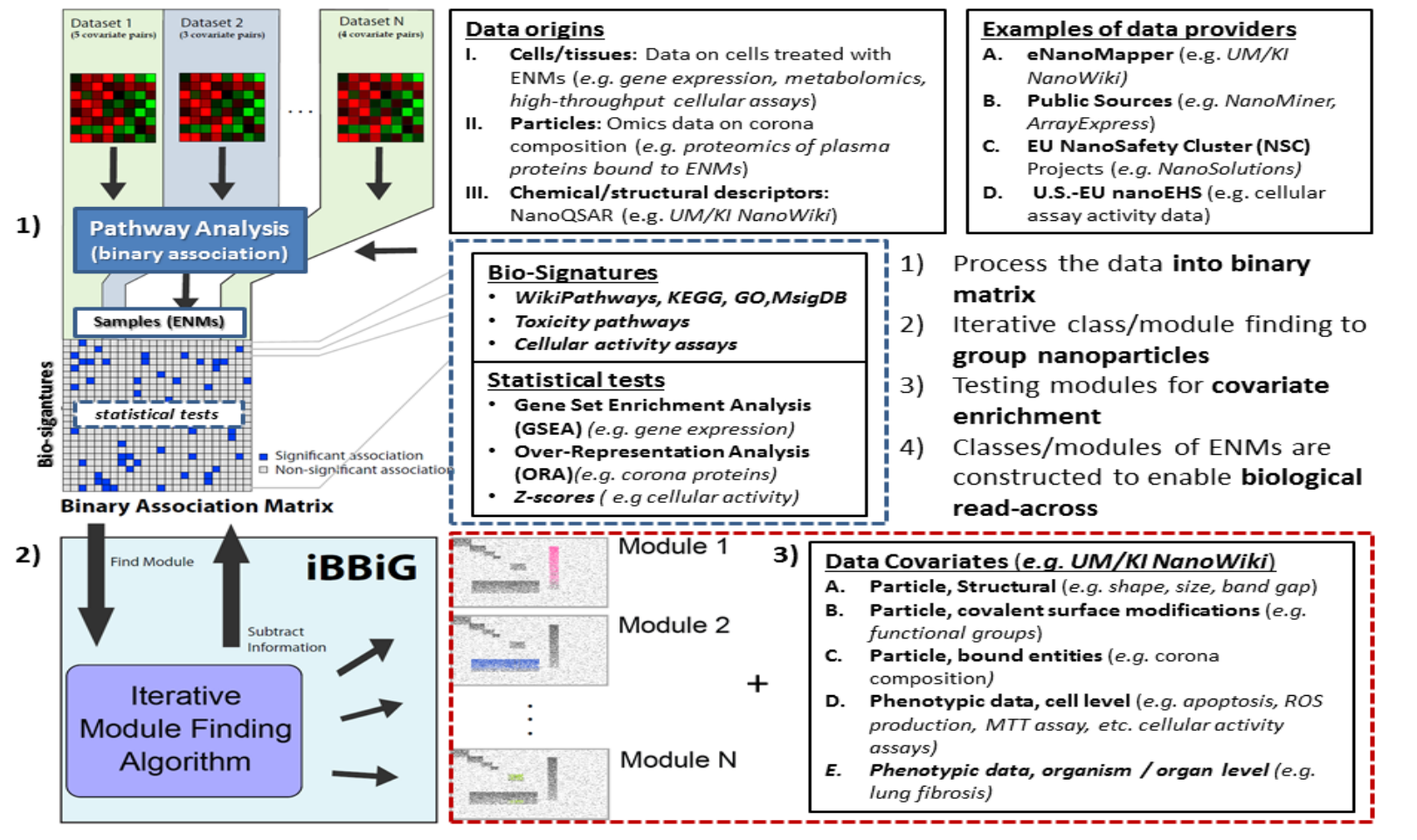


# Security



Use Open Standards on Resources but with extensive Authorisation and Authentication facilities accompanied by confidential data policies. e.g. *Validation against Confidential Data Case implemented Spring 2011*

# eNanoMapper starting 2014: OpenTox/ToxBank applied to Nano



What is the African vision for the environment?  
What can predictive toxicology methods do to progress it?



OpenTox Workshop, SETAC Africa, 2011

# 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 2011

## Innovation in Predictive Toxicology

Modeling, Applications, REACH, Risk Assessment

9-12 August, 2011

Technical University of Munich, Germany

---

Ca. 80 attendees participated in workshop,  
knowledge cafés, conference, poster session

More Information at:

[www.opentox.org/meet/opentox2011](http://www.opentox.org/meet/opentox2011)

There will be OpenTox 2014 workshops  
and meetings...!



## Upcoming OpenTox Meetings

September 2014 - Athens, Greece

November 2014 - John Hopkins, Baltimore

September 2015 - Dublin, Ireland

October 2015 - Miami beach, Florida

Discussing a first OpenTox Asia...

# Collaborating Partners

In Silico Toxicology,  
Switzerland

Douglas Connect,  
Switzerland  
(Coordinator)

Albert Ludwigs University  
Freiburg, Germany

Ideaconsult,  
Bulgaria



National Technical  
University of Athens,  
Greece

Istituto Superiore  
di Sanità, Italy

Fraunhofer Institute  
for Toxicology &  
Experimental Medicine,  
Germany

Technical University  
of Munich, Germany

David Gallagher, UK

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Chemistry of the Russian  
Academy of Medical  
Sciences, Russia

Seascope Learning &  
JNU, India



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**DouglasConnect**

*in silico* toxicology



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NIBSC-HPA*

*Ideaconsult Ltd*