

Satisfying REACH requirements with OpenTox

Barry Hardy (Douglas Connect, Switzerland)
OpenTox Coordinator

CADASTER Workshop
Maribor, Slovenia
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Introduction

OpenTox has developed an open semantic web for predictive toxicology. (2008-2011: Let's call it OpenTox 1.0)

Today I will:

- a) review the OpenTox 1.0 framework within the context of REACH;
- b) present some recent developments on OpenTox services and applications and what they can do.

The OpenTox Framework (reported 2010)

Collaborative development of predictive toxicology applications

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

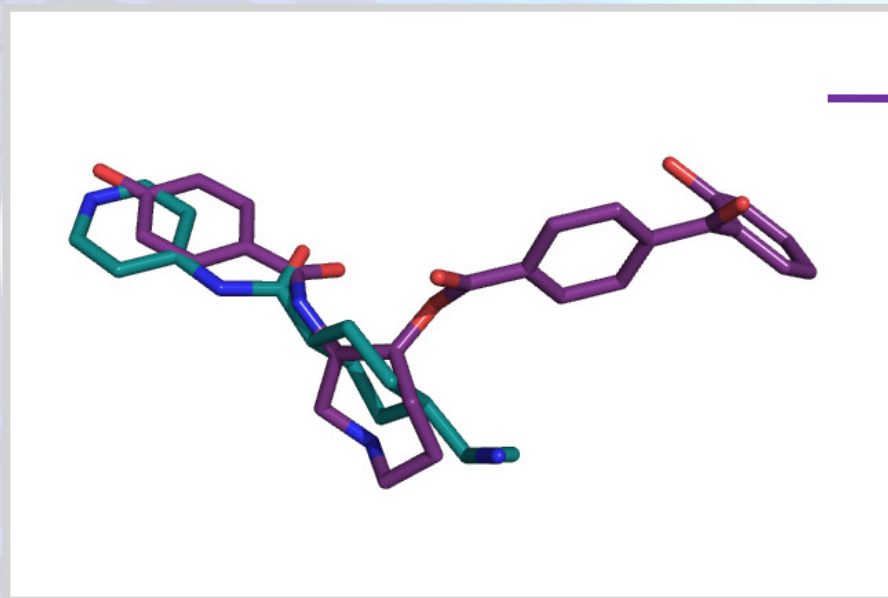
Barry Hardy, Nicki Douglas, Christoph Helma, Micha Rautenberg, Nina Jeliaskova, Vedrin Jeliaskov, Ivelina Nikolova, Romualdo Benigni, OlgaTcheremenskaia, Stefan Kramer, Tobias Girschick, Fabian Buchwald, Joerg Wicker, Andreas Karwath, Martin Gutlein, Andreas Maunz, Haralambos Sarimveis, Georgia Melagraki, 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

Most accessed paper in last year!

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

Satisfying REACH Information Gathering Requirements

Input Structure



VO

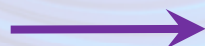


Out - Toxic or Not?

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

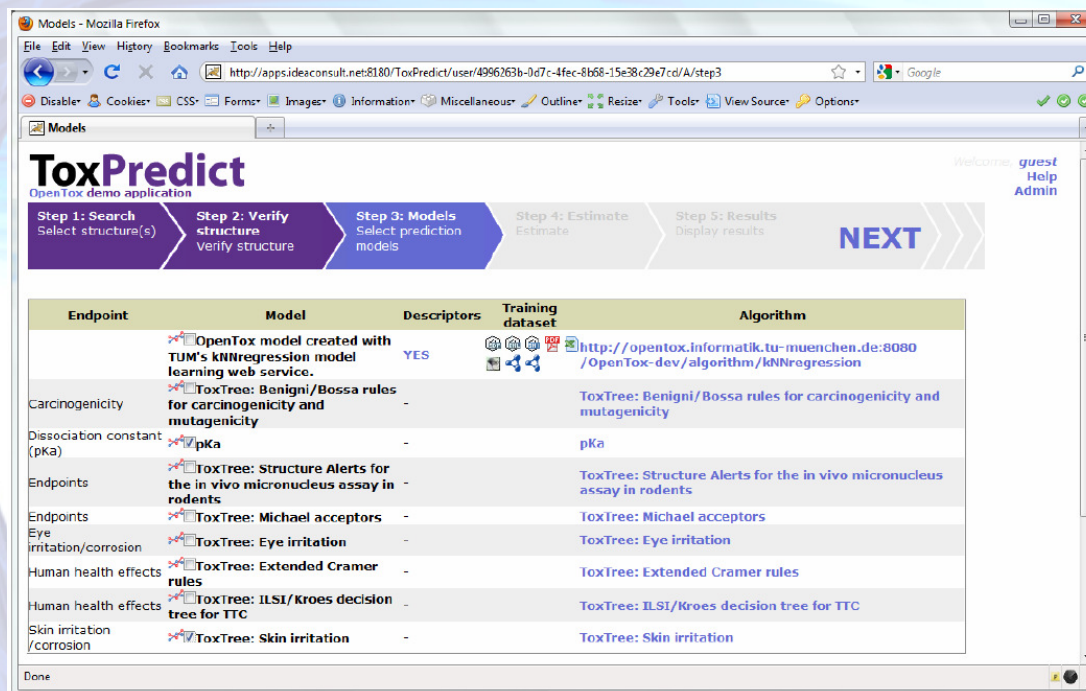


Driver



Increasing demands on industry to satisfy safety evaluation and risk assessment required by REACH legislation. (Over 140k cmpds registered).

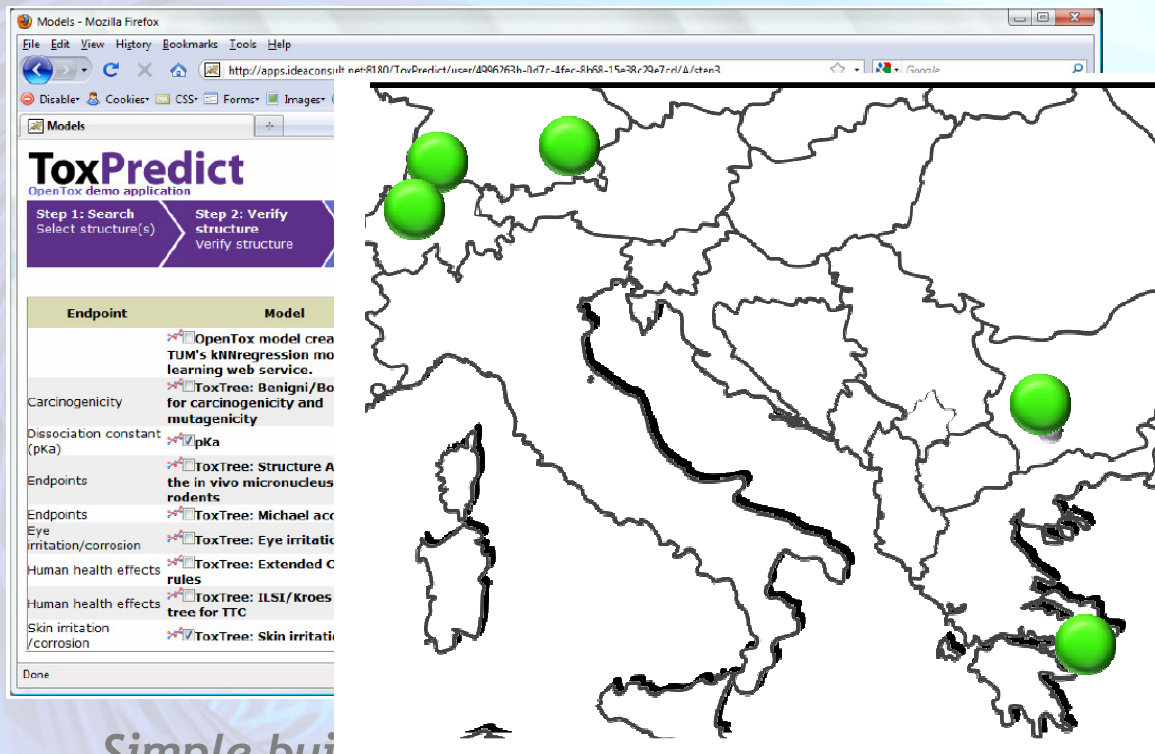
With OpenTox approach to standards you can reliably gather information from multiple resources in real time...



Endpoint	Model	Descriptors	Training dataset	Algorithm
	OpenTox model created with TUM's kNNregression model learning web service.	YES	http://opentox.informatik.tu-muenchen.de:8080/OpenTox-dev/algorithm/kNNregression	
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

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

ToxPredict accesses linked resources ...



ToxPredict
OpenTox demo application

Step 1: Search
Select structure(s)

Step 2: Verify
structure
Verify structure

Endpoint	Model
	OpenTox model creation TUM's kNN regression machine learning web service.
Carcinogenicity	ToxTree: Benigni/Bo for carcinogenicity and mutagenicity
Dissociation constant (pKa)	ToxTree: pKa
Endpoints	ToxTree: Structure A the in vivo micronucleus rodents
Endpoints	ToxTree: Michael acc
Eye irritation/corrosion	ToxTree: Eye irritati
Human health effects	ToxTree: Extended C rules
Human health effects	ToxTree: ILSI/Kroes tree for TTC
Skin irritation /corrosion	ToxTree: Skin irritati

Done

Simple built-in
application
methods and

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

Or Taverna workflows can be run for more complex tasks..

The image shows two overlapping windows. The background window is the ToxPredict web application in a Mozilla Firefox browser. It displays a map of Europe with three green circles highlighting specific regions. The foreground window is the Taverna Workflow editor, showing a complex workflow diagram with various tasks like 'ask_username', 'calculate_descriptors', 'learn_model', and 'apply_model_to_testset' connected by arrows. The Taverna interface includes a 'Service panel' on the left and a 'Workflow explorer' on the right.

ToxPredict
OpenTox demo application

Step 1: Search
Select structure(s)

Step 2: Verify
Verify structure

Endpoint	Model
Carcinogenicity	OpenTox model creat TUM's kNNregression mod learning web service.
Dissociation constant (pKa)	ToxTree: Benigni/Bos for carcinogenicity and mutagenicity
Endpoints	ToxTree: Structure Al the in vivo micronucleus rodents
Endpoints	ToxTree: Michael acc
Eye irritation/corrosion	ToxTree: Eye irritatio
Human health effects	ToxTree: Extended Cr rules
Human health effects	ToxTree: ILSI/Kroes tree for TTC
Skin irritation /corrosion	ToxTree: Skin irritatio

Done

Taverna Workflow editor interface showing a workflow diagram with tasks like 'ask_username', 'calculate_descriptors', 'learn_model', and 'apply_model_to_testset'.

Simple building
applications
methods and

Distributed a
wide range o
methods

Integration into workflow systems
for computational biology

A Toxicology Ontology Roadmap

Submitted 31 Aug 2011: 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

OpenTox - CADAster Collaboration

CADAster web site uses applicability domain and substructure / similarity search facilities via the OpenTox API compliant web services, running at apps.ideaconsult.net:8080/ambit2

The applicability domain algorithms used are: apps.ideaconsult.net:8080/ambit2/algorithm?type=AppDomain

The results are displayed integrated within the Cadaster web database www.cadaster.eu/database/static/home.do

OpenTox - CADAster Collaboration

Planned Developments:

1. Providing an OpenTox API wrapper for CADAster Soap web services (Nina Jeliazkova, Ideaconsult)
2. Integrating CADAster models in ToxPredict, via the OpenTox API wrapper (Nina Jeliazkova, Ideaconsult)
3. Provide access to selection of OpenTox models via CADAster web site
(Igor Tetko, Helmholtz Centre Munich)

REACH Requirements



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 lack of well established (Q)SAR software

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)

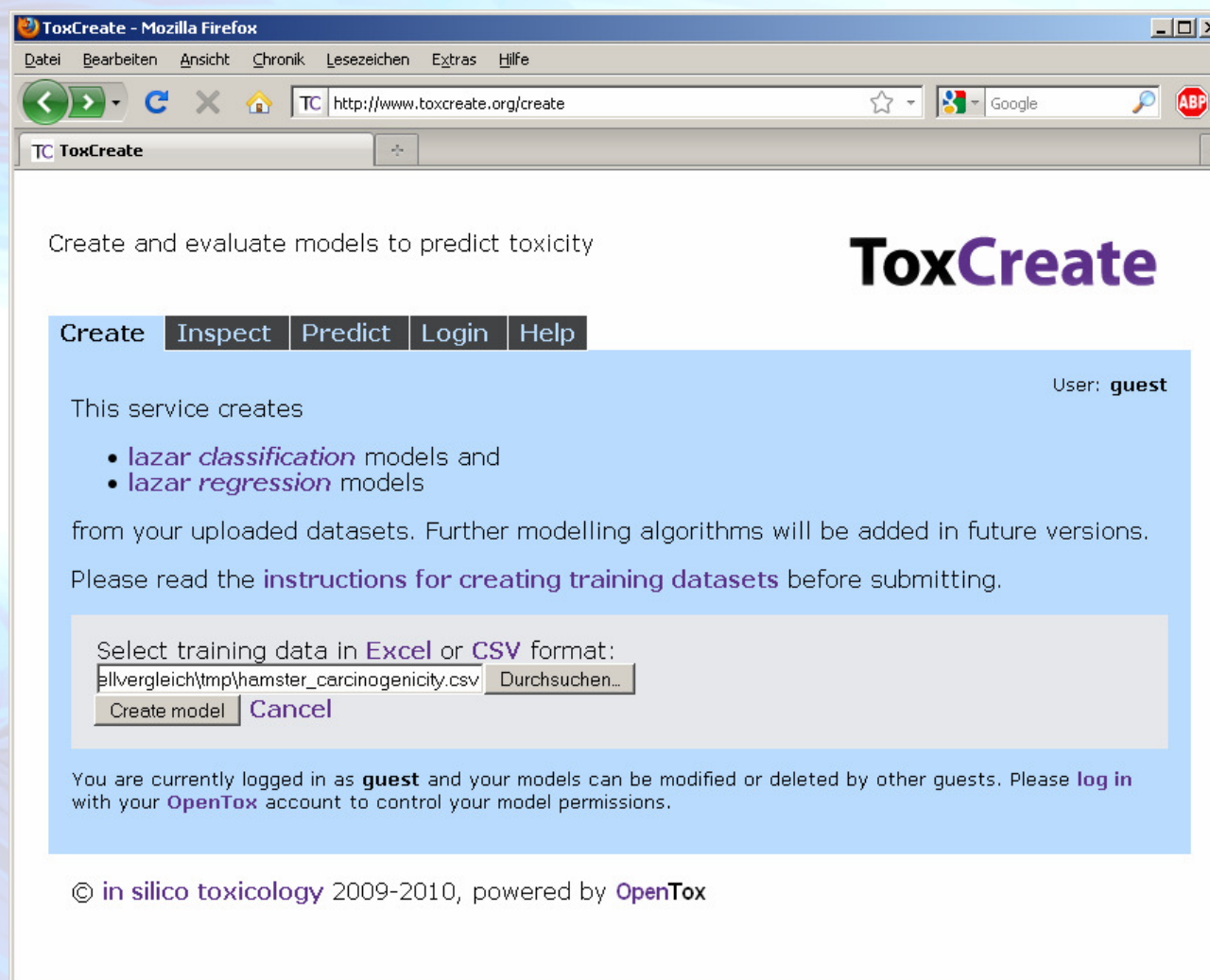
(Q)SARs & REACH requirements

(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 the ToxCreate web application running in a Mozilla Firefox browser. The browser's address bar displays the URL <http://www.toxcreate.org/create>. The page title is "ToxCreate". The main heading reads "Create and evaluate models to predict toxicity". Below this, there is a navigation bar with tabs: "Create", "Inspect", "Predict", "Login", and "Help". The "Create" tab is currently selected. The page content area has a light blue background and includes the text "This service creates" followed by a bulleted list: "• *lazar classification* models and" and "• *lazar regression* models". Below the list, it states "from your uploaded datasets. Further modelling algorithms will be added in future versions. Please read the [instructions for creating training datasets](#) before submitting." A text input field is labeled "Select training data in [Excel](#) or [CSV](#) format:" and contains the file path "allvergleich\trmp\hamster_carcinogenicity.csv". To the right of the input field is a "Durchsuchen..." button. Below the input field are two buttons: "Create model" and "Cancel". In the top right corner of the content area, it says "User: guest". At the bottom of the content area, a message 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." The footer of the page reads "© [in silico toxicology](#) 2009-2010, powered by [OpenTox](#)".

www.ToxCreate.org developed by In Silico Toxicology

ToxCreat - (Q)SAR Model Results

ToxCreat - Mozilla Firefox

Datei Bearbeiten Ansicht Chronik Lesezeichen Extras Hilfe

TC http://www.toxcreate.org/models

TC ToxCreat

Create and evaluate models to predict toxicity

ToxCreat

Create Inspect Predict Login Help

User: guest

Get an overview about ToxCreat 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

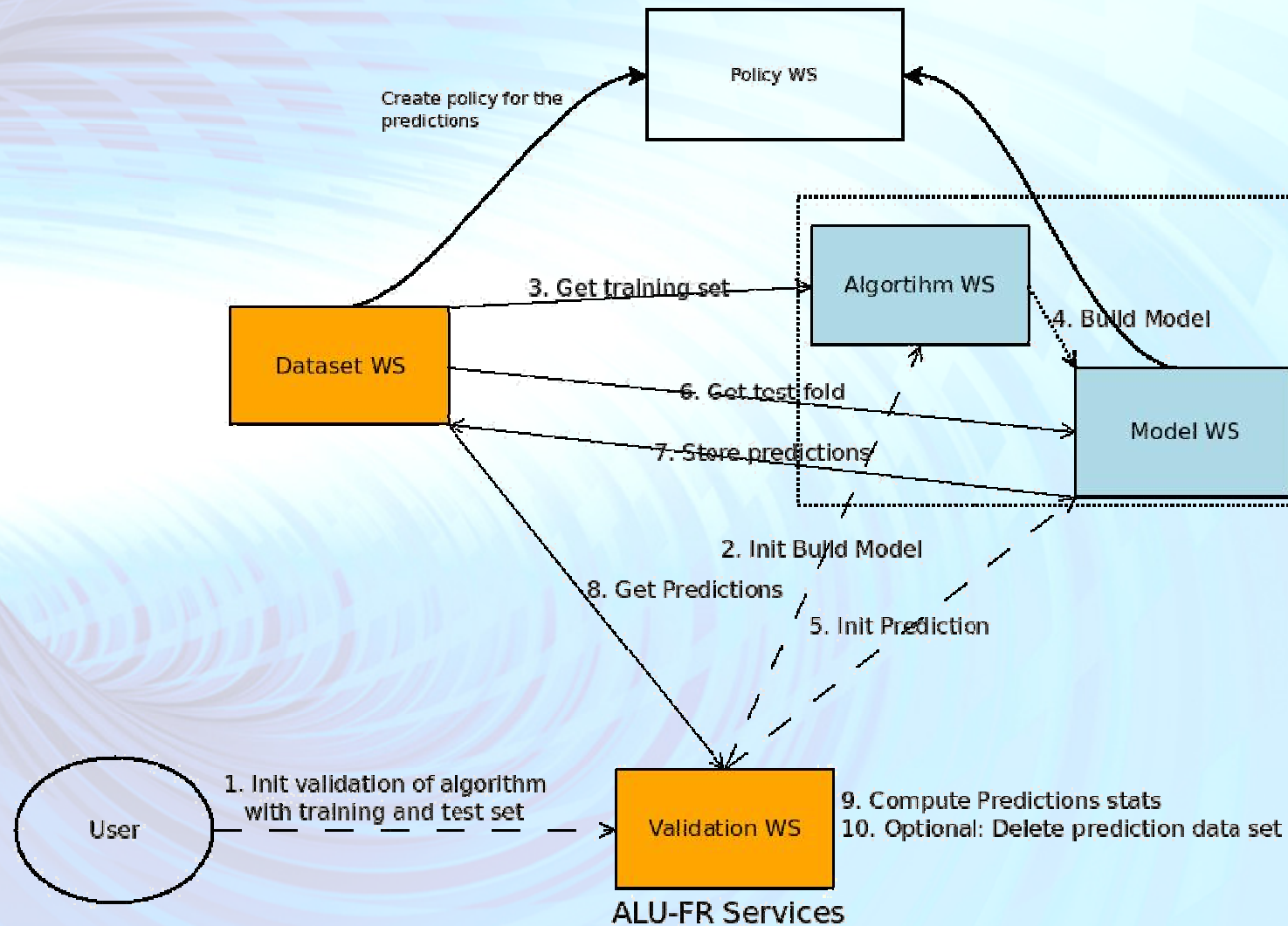
Confusion Matrix:

		Measured	
		active	inactive
Predicted	active	32	5
	inactive	7	25

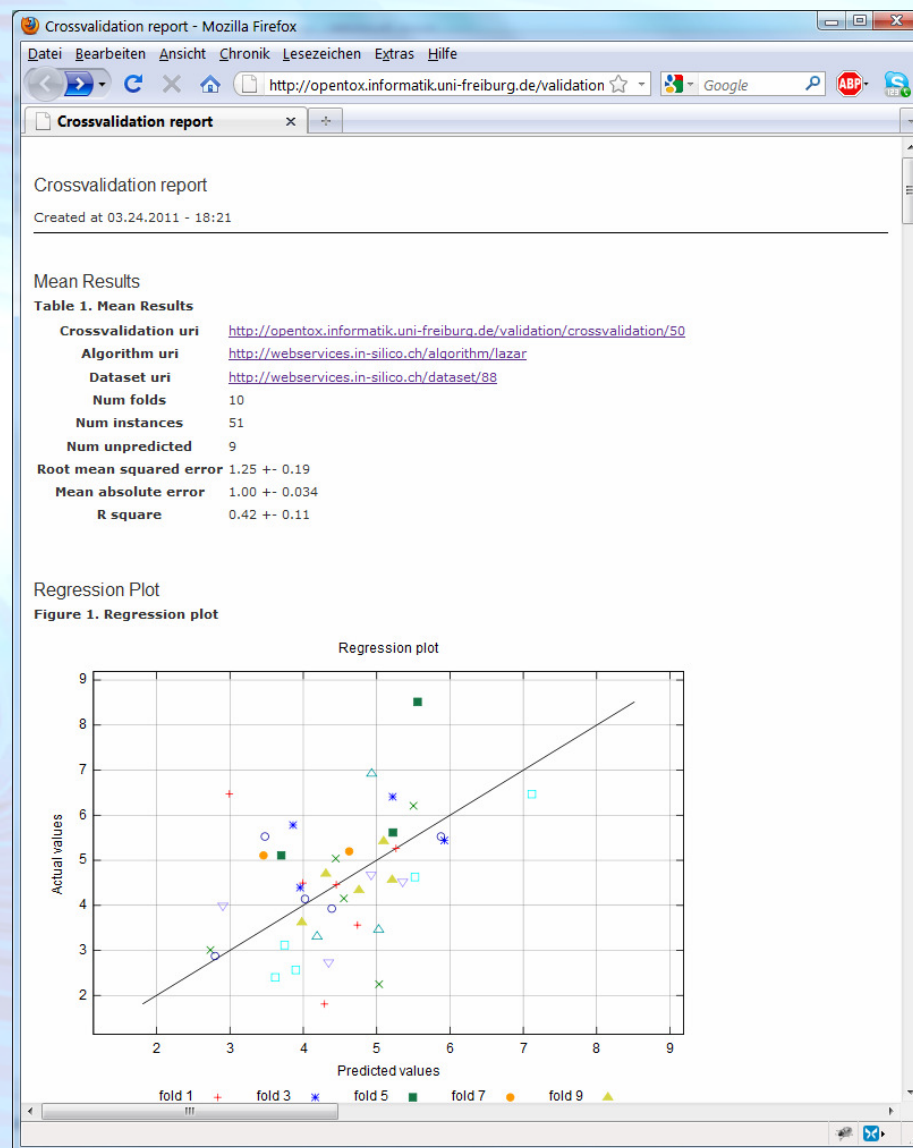
© in silico toxicology 2009-2010, powered by OpenTox

	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

Datei Bearbeiten Ansicht Chronik Lesezeichen Extras Hilfe

TC http://www.toxcreate.org/lazar#lazar_algorithm

TC ToxCreate phenylhydrazine (CHEBI:27924)

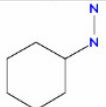
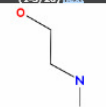
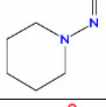
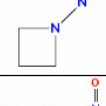
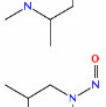
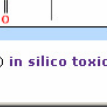
Create and evaluate models to predict toxicity

ToxCreate

Create Inspect **Predict** Login Help

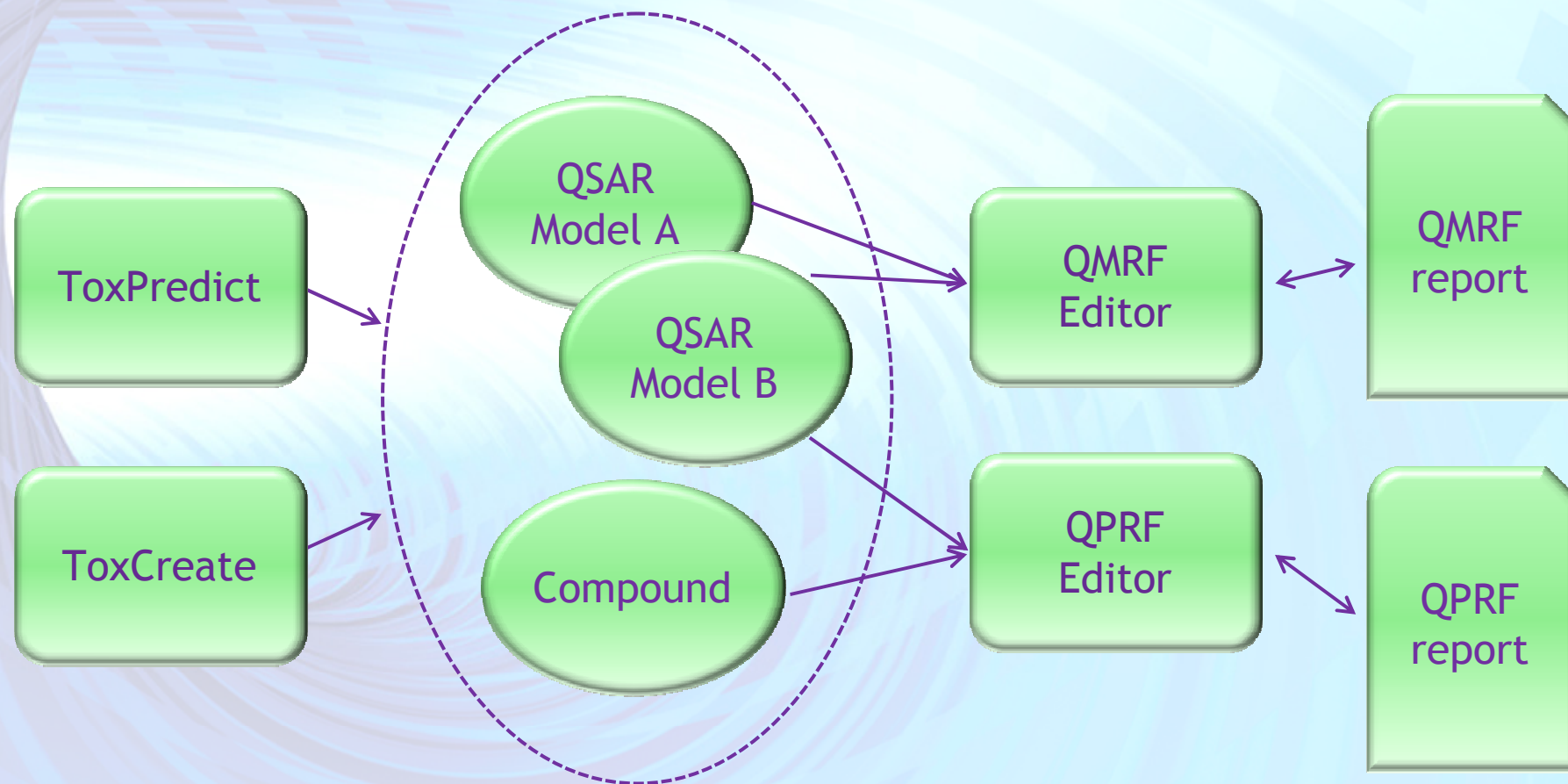
User: guest

New prediction

Hamster Carcinogenicity	Prediction	Confidence	Supporting information
	active	0.108	Names and synonyms Significant fragments
Neighbors (1-5/26) 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 1.2

Section 1. Name (Q)SAR Model Reporting Format

Section 1. Author Joint Research Centre, European Commission

Section 2. Date July 2007

Section 2. Contact Joint Research Centre, European Commission

Section 3. Email qsar.db@jrc.it

Section 4. www <http://ecb.jrc.ec.europa.eu/qsar/>

Section 5.

Section 6.

Section 7. **Background**

Section 7. The set of information that you provide will be used to generate (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

<http://ecb.jrc.ec.europa.eu/qsar/>

OK Abbrechen

QPRF Reporting (Qedit)

The screenshot displays the Qedit application interface. The main window has tabs for 1. Substance, 2. General Information, 3. Prediction, and 4. Adequacy Info. The Prediction tab is active, showing the Applicability Domain section. This section includes fields for the Name Applicability Domain Estimation Algorithm Used and a Link to Applicability Domain Resource. Below this is the 3.3.b. Structural Analogues section, which features a list of structural analogues (URIs) and a similarity level of 0.95. The list includes compounds like phenobarbital, 5-methyl-5-phenylbarbiturate, and calcium bis[5-(1-cyclohexen-1-yl)-5-ethylbarbiturate]. A chemical structure of calcium bis[5-(1-cyclohexen-1-yl)-5-ethylbarbiturate] is shown in the center. The bottom section is labeled Discussion, with an Applicability Domain Result of Metabolic Domain. A Compound Details window is open on the right, showing fields for URI, Smiles, InChI, InChI Key, CAS number, Chemical Name, EINECS, and REACH Reg. Date. It also lists available conformers with their respective URIs.

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: 0.95 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-phenylbar...	
primidone, Primaclo...	
calcium bis[5-(1-cyc...	
5-ethyl-5-(4'-hydrox...	
barbexalone	
1,3-dimethyl-5-phen...	
5-ethyl-5-phenylbar...	
N-(cyclohexylmethyl)...	

Image of structural analogue

3.3.c. Consideration

Discussion

Applicability Domain Result:

3.3.a. Choose Domain : Metabolic Domain

Compound Details

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

Smiles: [Ca+2].CCC1(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: 143-76-0

Chemical Name: calcium bis[5-(1-cyclohexen-1-yl)-5-ethylbarbiturate]

Einecs: 205-610-2

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>

Close Apply Changes and Close

Application by Pantelis Sopasakis (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.

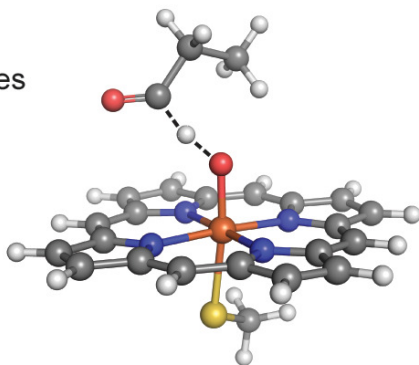
Metabolites, Metabolic Enzymatic induction and the creation of Reactive Intermediates may all lead to toxicity, e.g., in drug-drug interactions and hepatotoxic adverse events.

SMARTCyp Service for Predicting Metabolites

Atom Reactivity Library

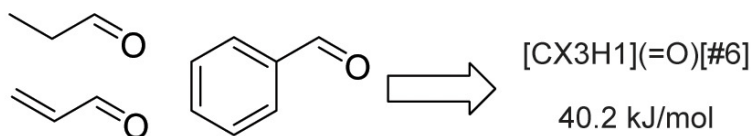
A. Calculate Quantum Chemical Reference Energies

Calculate transition state energies using density functional theory



B. Define SMARTS Rules

Group calculations by fragments and calculate average energies

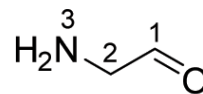


SMARTCyp - developed by Patrik Rydberg, University of Copenhagen

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

SMARTCyp

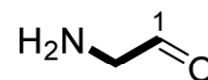
1. Assign Energies By SMARTS matching



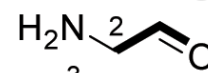
Atom	SMARTS	Energy
1	[CX3H1](=O)[#6]	40.2
2	[CX4][N]	39.8
3	[N^3][H1,H2]	54.1

2. Compute Accessibility Descriptor

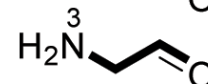
$$A_i = \text{Maxbonds}_i / \text{Maxbonds}_{\text{all}}$$



$$A_1 = 2 / 3 = 0.67$$



$$A_2 = 2 / 3 = 0.67$$



$$A_3 = 3 / 3 = 1.00$$

3. Compute Score and Rank Atoms

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

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

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

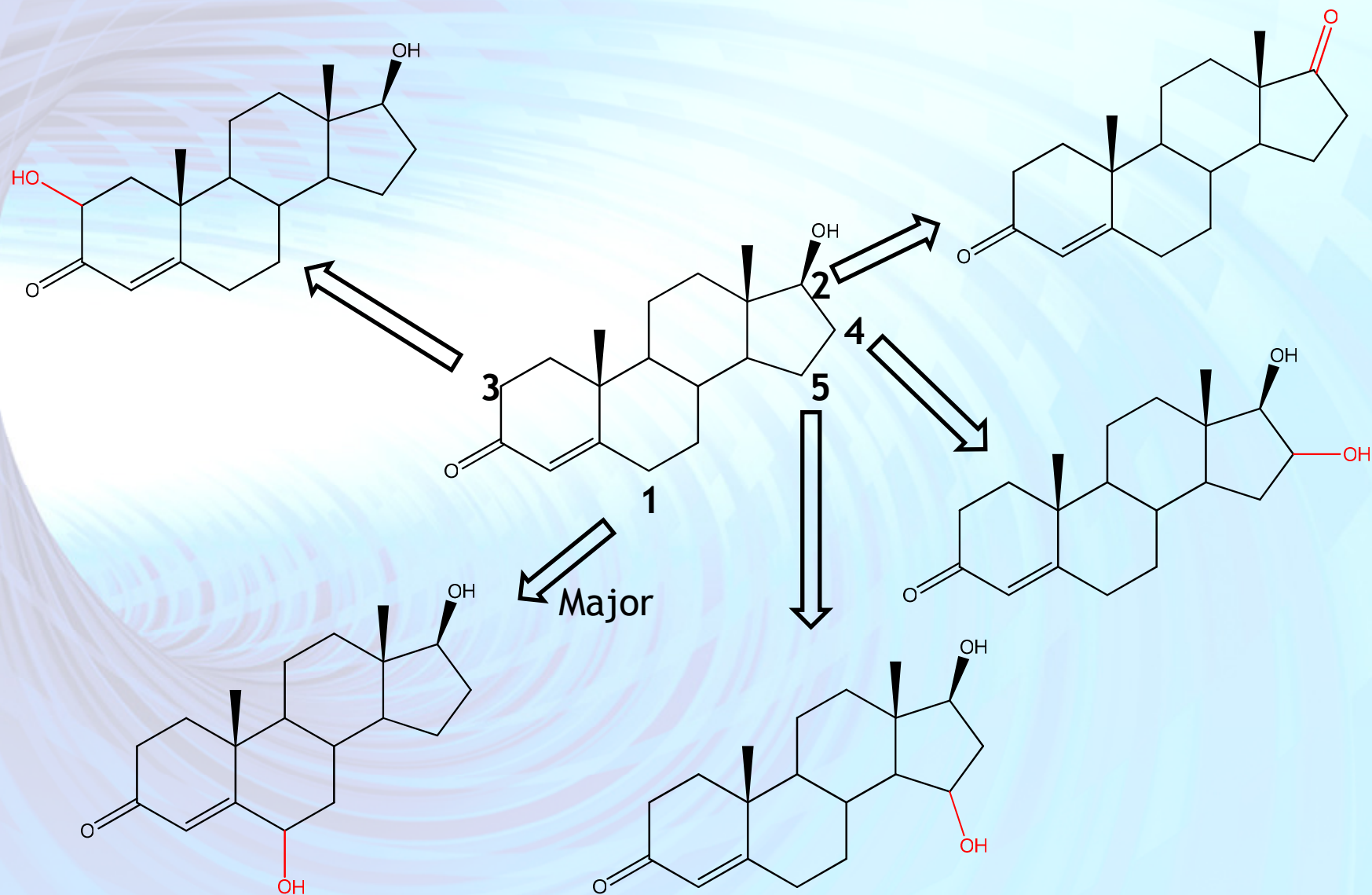
$$S_3 = 54.1 - 8 \cdot 1.00 = 46.10$$

Atom 1 - Rank 2

Atom 2 - Rank 1

Atom 3 - Rank 3

SmartCYP Prediction of Testosterone Metabolites



Metabolites

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

ambit

Search by property or identifier name (optional) and value

This site and AMBIT REST services are under development!

idconformer=773441

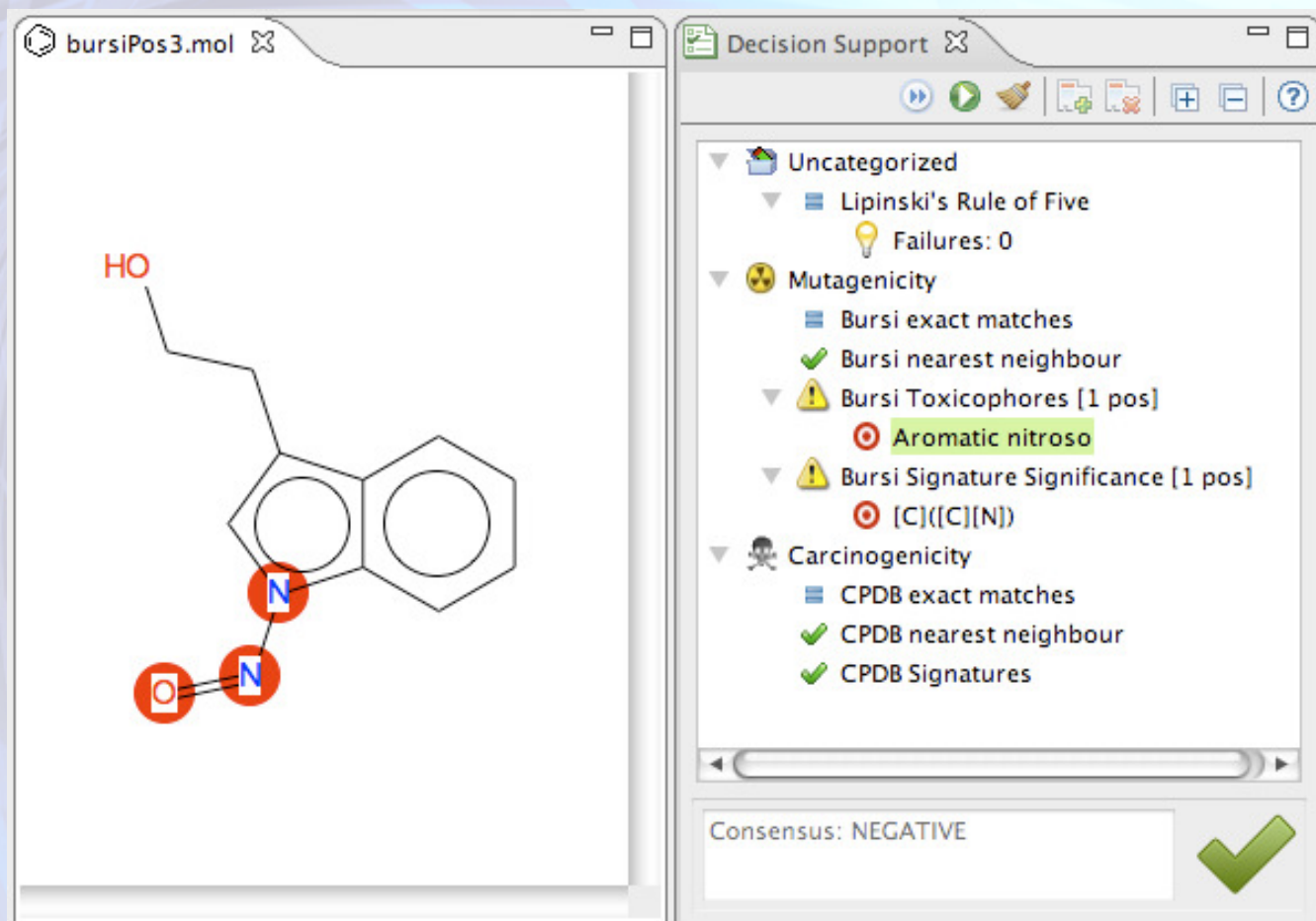
☒

Chemical structure diagram showing a benzene ring with a carboxylic acid group and a side chain containing a nitrogen atom. The structure is annotated with colored circles indicating potential metabolic sites: orange for aliphatic hydroxylation, green for aromatic hydroxylation, pink for N-dealkylation, brown for N-oxidation, orange for O-dealkylation, and blue for S-oxidation.

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

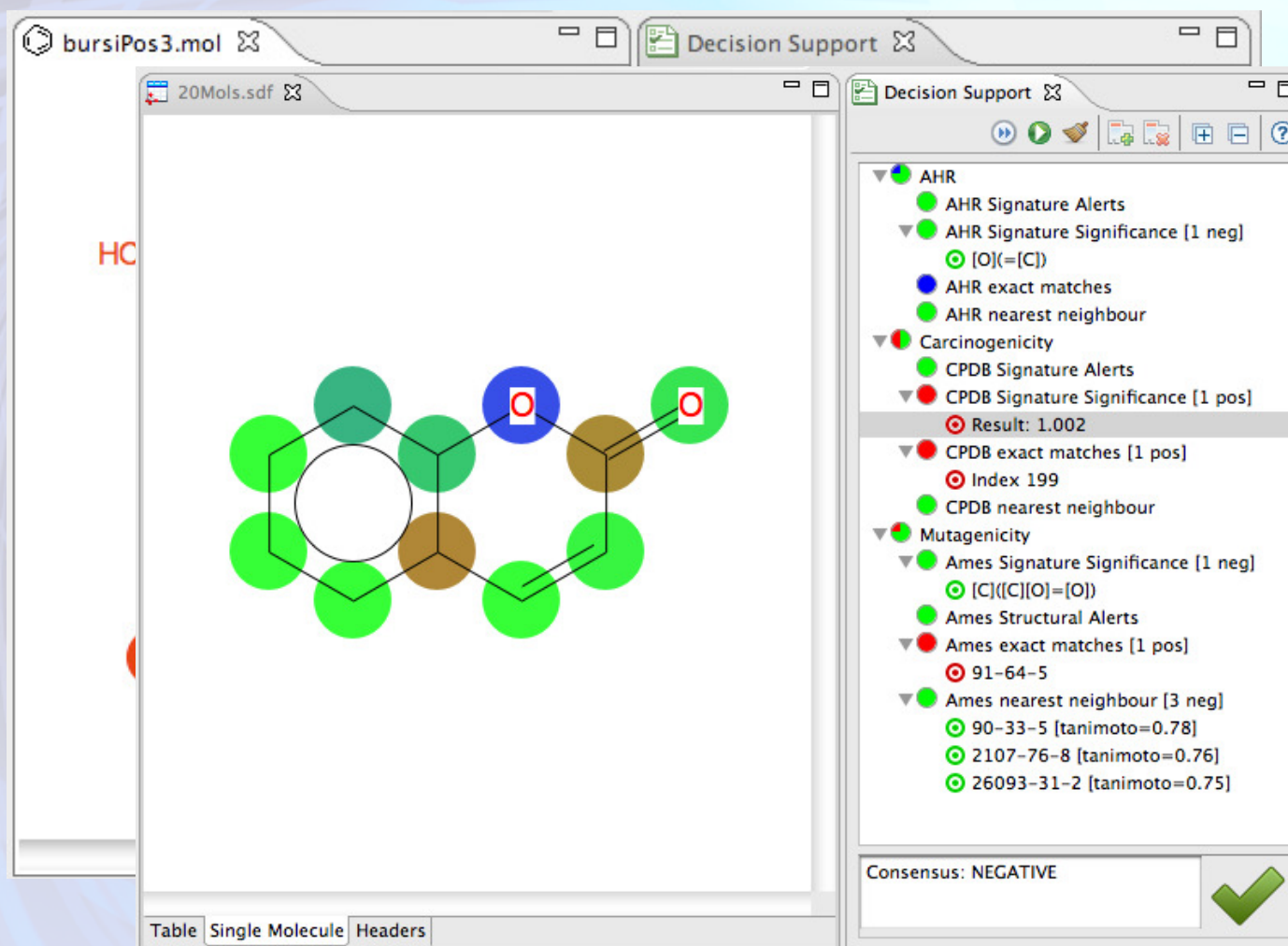
Developed by Ideaconsult

Bioclipse Visualisation Workbench



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

Bioclipse Visualisation Workbench



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

Bioclipse Visualisation Workbench - OpenTox

The screenshot displays the Bioclipse Visualisation Workbench interface. The central window shows a chemical structure of a steroid-like molecule with an epoxide group highlighted in red. The word "Changed" is written in purple above the structure. To the left, a sidebar lists "Sample Data Test1", "Test8H1", and "Virtual". Below the structure, a "Properties" table is visible:

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

On 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 decision support panel, a "2D-Structure" window is partially visible. A sidebar on the far right lists "Samples [4 SM...]" with checkboxes for "Amino acid", "Epoxide [*[C", "Ester [O=C(*", and "t-Butyl [*[C(".

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

Read-Across Application

Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://localhost:8085/vtox#Categories

http://localhost:8085/vtox#Login

Help

Page: 0 Show identifiers Show categories Assign categories Download

Property

Source chemical

Target chemical

Select Structures	1	2	3	4	5
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

Neutral Organics (alcohol) YES YES YES YES YES

Neutral Organics (ether) YES YES YES YES YES

Developed by Ideaconsult Ltd. 2011

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

Find: skin Next Previous Highlight all Match case

Done

Read-Across Application

Firefox browser window showing the ToxPredict application interface. The URL is <http://localhost:8080/properties>.

The interface displays chemical structures and their properties for five compounds. The compounds are:

- 1: 1-butoxypropan-2-ol
- 2: 1-propoxypropan-2-ol
- 3: 1-ethoxypropan-2-ol
- 4: Propylene glycol
- 5: 1-methoxypropan-2-ol

The properties table includes:

Property	1	2	3	4	5
Select Structures	Yes	Yes	Yes	Yes	Yes
CASRN	5131-66-8	1569-01-3	1569-02-4	57-55-6	107-98-2
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		203-539-1
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	90.12
Octanol-water_partition_coeff					
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 REPUSSION	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	90.12
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

The Matrix Plot section shows a grid of plots for the compounds, with a 'Zoom' button for each plot.

Read-Across Application

Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://localhost:8085/vtox#Toxicity

http://localhost:8085/vtox#Login

chembi id

Help

Page: 0

Show identifiers Show data Show predictions Run models Download

Property

1 2 3 4

Carcinogenicity

Dataset	1	2	3	4	5
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					ND
Rat_Male_NTP					ND
Reference					CPDB
SAL					

Model

Model	1	2	3	4	5
Potential S. typhimurium TA100 mutagen based on QSAR	NO	NO	NO	NO	NO
Potential carcinogen based on QSAR	NO	NO	NO	NO	NO
Structural Alert for genotoxic carcinogenicity	NO	NO	NO	NO	NO
Structural Alert for nongenotoxic carcinogenicity	NO	NO	NO	NO	NO
Unlikely to be a S. typhimurium TA100 mutagen based on QSAR	NO	NO	NO	NO	NO
Unlikely to be a carcinogen based on QSAR	NO	NO	NO	NO	NO

EPA Integrated Risk Information System (IRIS) Toxicity Review Data

Property	Value
Inhalation_RIC_Assessed	1.00
Inhalation_RIC_Confidence	Medium
Inhalation_RIC_CriticalEffects	mild reversible sedation NOAEL (No observed adverse effect level) HEC
Inhalation_RIC_Notes	
Inhalation_RIC_mg_per_m3	2.00
Inhalation_RIC_mmole_per_m3	0.02
Inhalation_StudyRoute	
Inhalation_UniRisk_Assessed	0.00
Inhalation_UniRisk_microg_m3	
Inhalation_UniRisk_micromole_m3	

Physico chemical properties >> Boiling point

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

Skin sensitisation

Model	1	2	3	4	5
Alert for Acyl Transfer agent identified	NO	NO	NO	NO	NO
Alert for Michael Acceptor identified	NO	NO	NO	NO	NO
Alert for SN2 identified	NO	NO	NO	NO	NO
Alert for SNAr 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:8085/am42/dataset/R11188

ToxPredict

WELCOME, GUEST

My account

Log out

PREDOCT

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

Read-Across Application

Firefox browser window showing ToxPredic interface.

Carcinogenicity

.Dataset

CAS				57-55-6	
Canc				1.00	
Mouse_Female_Canc				ND	
Mouse_Female_NTP				ND	
Mouse_Male_Canc				ND	
Mouse_Male_NTP				ND	
Rat_Female_Canc				1.00	
Rat_Female_NTP				ND	
Rat_Male_Canc				1.00	
Rat_Male_NTP				ND	
Reference				CPDB	
SAL				1.00	

.Model

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

Identified	NO	NO	NO	NO	NO
Alert for SN2 identified	NO	NO	NO	NO	NO
Alert for SNAr 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/ambid2/dataset/R11188

Chemical Space Visualisation (Ches-Mapper)



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

<http://opentox.informatik.uni-freiburg.de/ches-mapper>



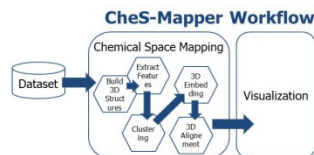
Martin Gütlein^{1*}, Andreas Karwath¹, Stefan Kramer²

*guetlein@informatik.uni-freiburg.de

¹Institute for Computer Science • Albert-Ludwigs-Universität Freiburg • Germany, ²Institute for Computer Science I12 • Technische Universität München • Germany

Abstract

Scientific researchers in the field of cheminformatics, are often overwhelmed by the size and the sheer complexity of chemical datasets. Therefore, the need for visualization tools, is one of the utmost requests. Our recently developed 3D molecular viewer Ches-Mapper (Chemical Space Mapper) includes many techniques, like state-of-the-art structural clustering, and multi-dimensional embedding techniques. Large datasets are divided into clusters of similar compounds and consequently arranged in 3D space, such that their spatial proximity reflects their chemical similarity. This intuitively provides essential information to the user, while making the dataset more easily accessible and allowing easy and understandable access to a large number of chemical structures within seconds. The different clustering approaches employed in our tool utilize common substructures as well as quantitative chemical descriptors of the compounds. These features can be highlighted within Ches-Mapper, which aids the chemist to better understand the underlying scientific knowledge. As a final function, the tools can also be used to select and export specific part of a given dataset for further analysis.



- The workflow is divided into Mapping and Visualization
- Mapping:
 - Is a preprocessing step where the data is clustered and arranged in 3D space
 - Easy to use, the novice user can employ default settings
 - Algorithms can be configured manually
 - Developers can plug in own algorithms
- Visualization:
 - The dataset is presented in a 3D viewer
 - The clustering and embedding provides relational information about similarity and makes the data easily accessible

Wizard Dialog to Control Mapping

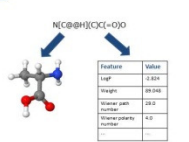
- A wizard dialog guides through the Mapping process
- Suitable for novice and expert users
- Single Steps:
 - Load dataset
 - Build 3D structure
 - Extract features
 - Clustering
 - 3D Embedding
 - 3D Alignment
- Automatic detection and plug in of new methods and algorithms



Chemical Space Mapping

Build 3D Structure and Extract Features

- Select input dataset
 - Various dataset formats are supported (csv/mol/smi/...)
 - 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



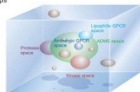
3D Embedding (of Clusters & Compounds)

- Embedding algorithms assign 3D coordinates to each compound or cluster, according to the feature values of the compounds
- Different approaches are provided:
 - Principal Component Analysis (PCA)
 - Multidimensional Scaling Using Majorization (SMACOF)
 - T-distributed Stochastic Neighbor Embedding (tSNE)
- Developers can easily plug in their own/preferred 3D embedding algorithm

Features	Length	Weight	Wt. path	Wt. polarity
CCCCC(=O)OCC=O	4.27	33.880	188.0	27.0
CCCCC(=O)OCC=O	4.27	33.880	188.0	27.0
CCCCC(=O)OCC=O	4.27	33.880	188.0	27.0
CCCCC(=O)OCC=O	4.27	33.880	188.0	27.0
CCCCC(=O)OCC=O	4.27	33.880	188.0	27.0

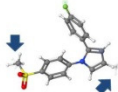
Cluster Compounds

- 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's single cluster
 - Sequentially merge similar clusters
 - Structural Clustering
 - Finds groups that share structural similarity
 - Compounds are assigned to clusters when there exists a common subgraph of sufficient size
- Developers can plug in new cluster algorithms



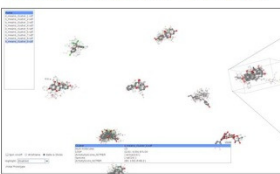
3D Alignment of Compounds

- Compounds in a cluster are likely to share common subgraphs:
 - This subgraph is already available if structural clustering is performed
 - Alternatively, the maximum common subgraph can be computed within each cluster
- The compounds within a cluster can be superimposed/aligned according to this subgraph:
 - This shows differences between compounds



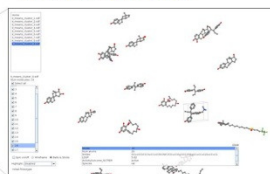
3D Visualization

Dataset Overview -- Clusters



- Datasets are separated into clusters, arranged in 3D space
- The intuitive interface of the 3D viewer allows to:
 - Zoom/rotate the clusters
 - Get valuable information on clusters via mouse over
 - Examine a cluster by clicking on it
- The embedding into 3D space (position/distance between clusters) reflects the similarity between clusters
- Cluster can be removed from the dataset

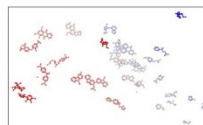
Inside Cluster View



- By selecting a cluster, the view zooms into the cluster and displays only the compounds included
- Details for each compound are available via mouse over
- Like the clusters, the compounds are embedded into the 3D space as well: the position/distance between compounds within the cluster reflects the similarity between compounds
- Compounds can be removed from the dataset

Highlight Features and Endpoints

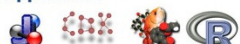
- All compound properties can be highlighted:
 - The compounds are colored according to the numeric value, a high value is indicated by red, a low value is indicated by blue
 - Also available for the cluster overview
- Gives an intuitive explanation towards the quality of the clustering approach:
 - "Does the clustering algorithm separate active from inactive compounds?"



Open-Source Webstart Application

- Java program that comes in two variants:
 - Java Web Start application (can directly start from a web browser)
 - Local installation that makes use of non-java libraries
- CheS-Mapper is available at <http://opentox.informatik.uni-freiburg.de/ches-mapper>

Powered by:



References

- [1] Seeland, M., Girschick, T., Buchwald, F., Kramer, S. Online Structural Graph Clustering Using Frequent Subgraph Mining, 2010, Machine Learning and Knowledge Discovery in Databases, 213–228, Springer
- [2] Jmol: an open-source Java viewer for chemical structures in 3D. <http://www.jmol.org>

Acknowledgements

This work has been supported by the EU FP7 project (HEALTH-F5-2006-200787) OpenTox (<http://www.opentox.org>).

Developed by Martin Gütlein, Andreas Karwath, Stefan Kramer (ALU & TUM)



Chemical Space Visualisation (Ches-Mapper)



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



Abstract

Scientific researchers in the field of cheminformatics, chemical datasets. Therefore, the need for visualization. Our recently developed 3D molecular viewer Ches-Mapper of the-art structural clustering, and multi-dimensional in 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 descriptors of the compounds. These features can be used to understand 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 (sdf/mol/mixed...)
 - 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 Compounds

- Compounds in the dataset are assigned to subgroups according to their similarity
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 - 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

- Java program that comes in two variants:
 - Java Web: Start application (can directly start)
 - Local installation that makes use of non-java
- CheS-Mapper is available at <http://opentox.info>

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: disabled

Initial Prototype

Cluster	k_means_cluster_9.sdf
Num molecules	19
LOGP	[2.81; 9.09] 0:5.09
ActivityOutcome_NCTRER	[active(19)]
Species	[rat(19)]
ActivityScore_NCTRER	[80; 100] 0:88.11

Forming chemical feature-based categories



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



Abstract

Scientific researchers in the field of chemoinformatics chemical datasets. Therefore, the need for visualizing the recently developed 3D molecular viewer CheS-Mapper of the 3D structural clustering, and multi-dimensional similarity 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 are used to understand the underlying scientific knowledge, a part of a given dataset for further analysis.

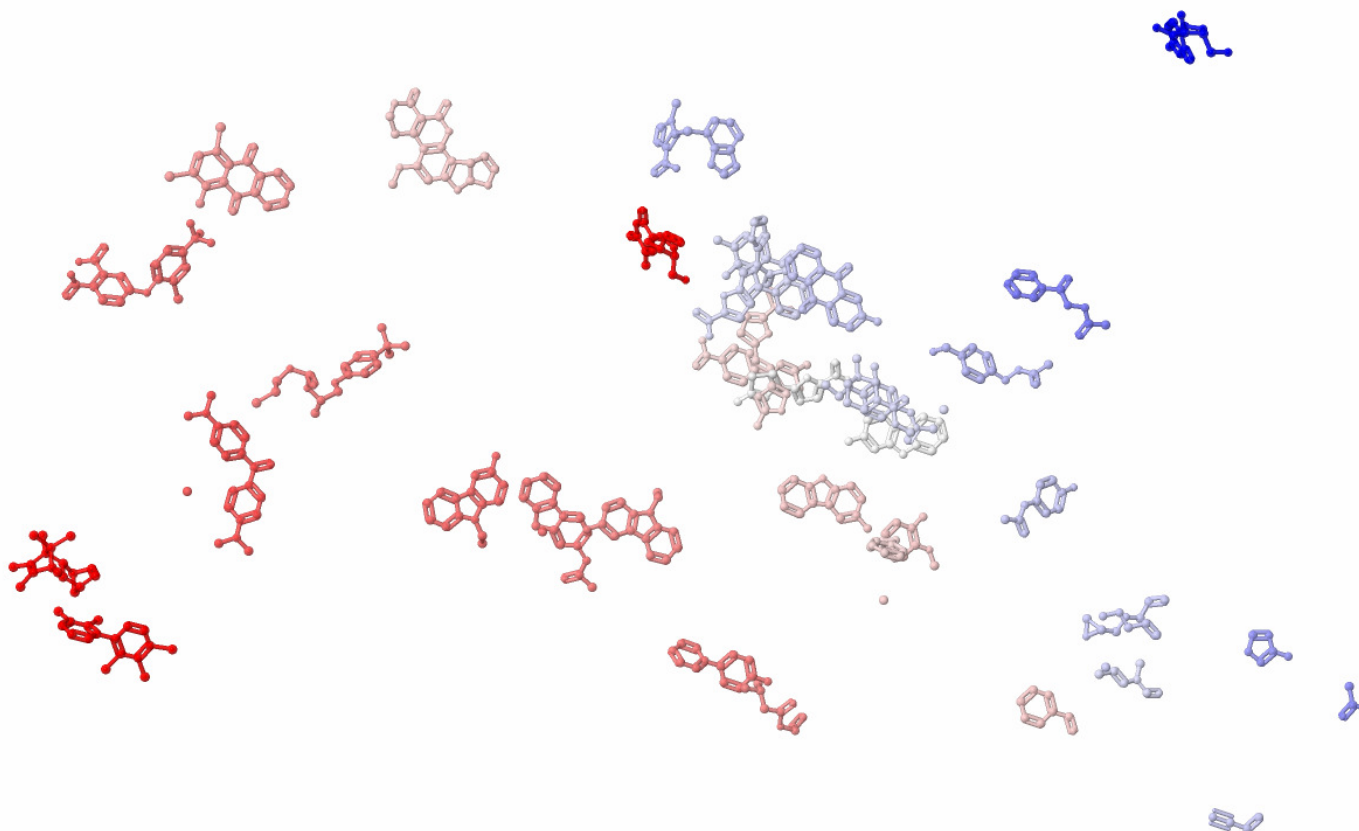
Build 3D Structure Extract Features

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 - 3D structure can be built with Chemical Development Kit (CDK) or OpenBabel
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 - k-Means Clustering
 - Fixed number of k clusters
 - Random initialization, iterative up-clusters and cluster centroids
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 - Each compound is single cluster
 - Sequentially merge similar clusters
 - Structural Clustering
 - Finds groups that share structural features
 - Compounds are assigned to clusters where there exists a common subgraph of size
- Developers can plug in new cluster algorithm

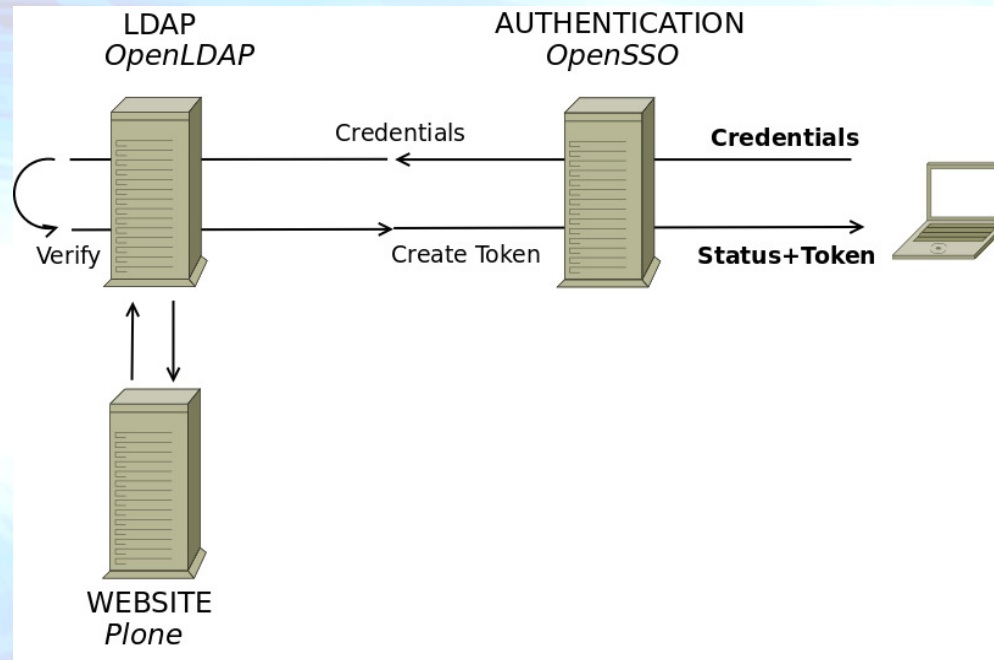
- Java program that comes in two variants:
 - Java Web Start application (can direct)
 - Local installation that makes use of no Java
- CheS-Mapper is available at <http://opentox.org>



Controlling Access to Confidential Information

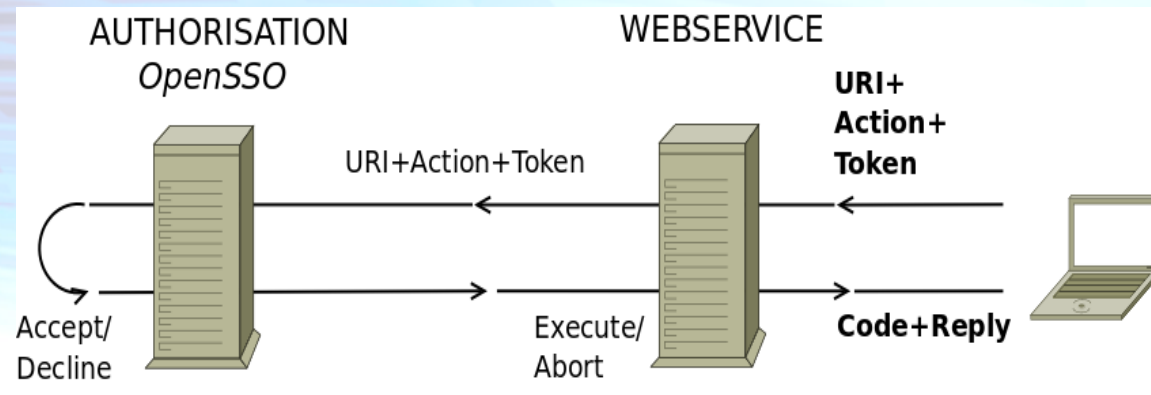
- OpenTox makes resources available through **URIs**
- OpenTox provides facilities to protect confidential information located at **URIs**. Two tasks are involved here:
 - **Authentication**: Confirming the identity of the user requesting access
 - **Authorisation**: Granting the confirmed identity access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

Authentication



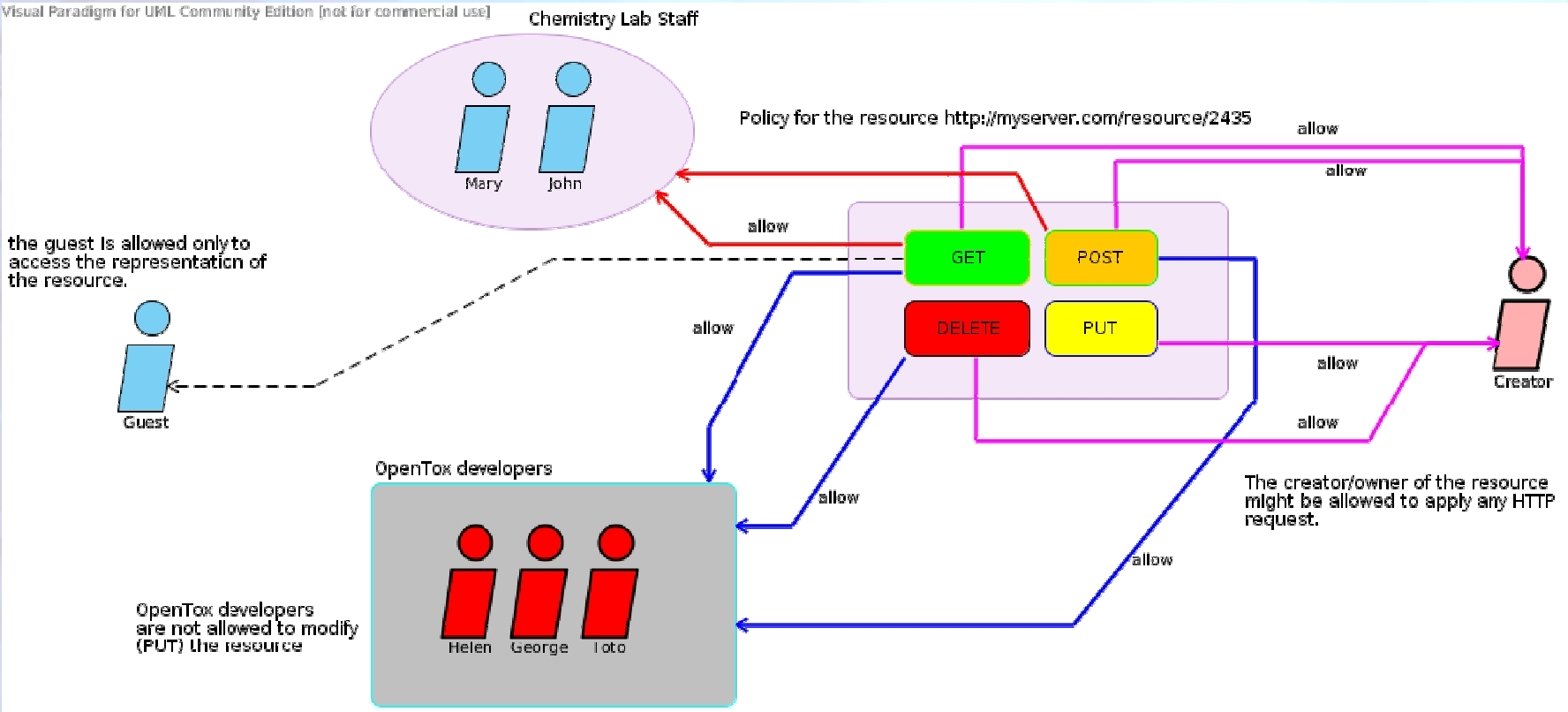
- Registered users are instantly available as potential users of OpenTox web services
- Users receive a token upon service request

Authorisation



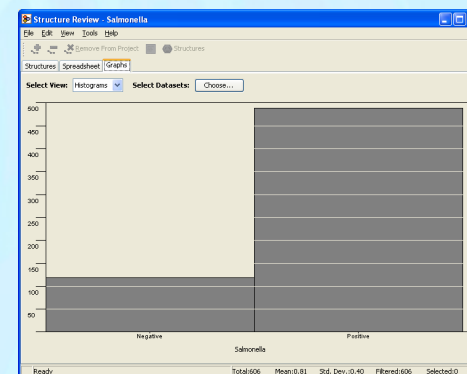
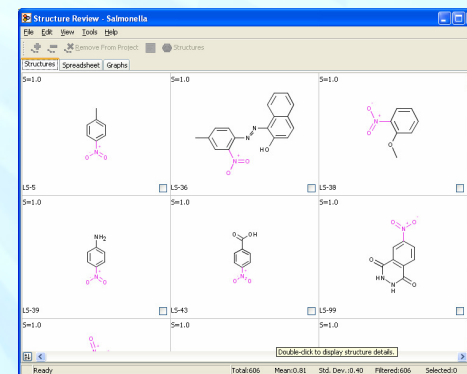
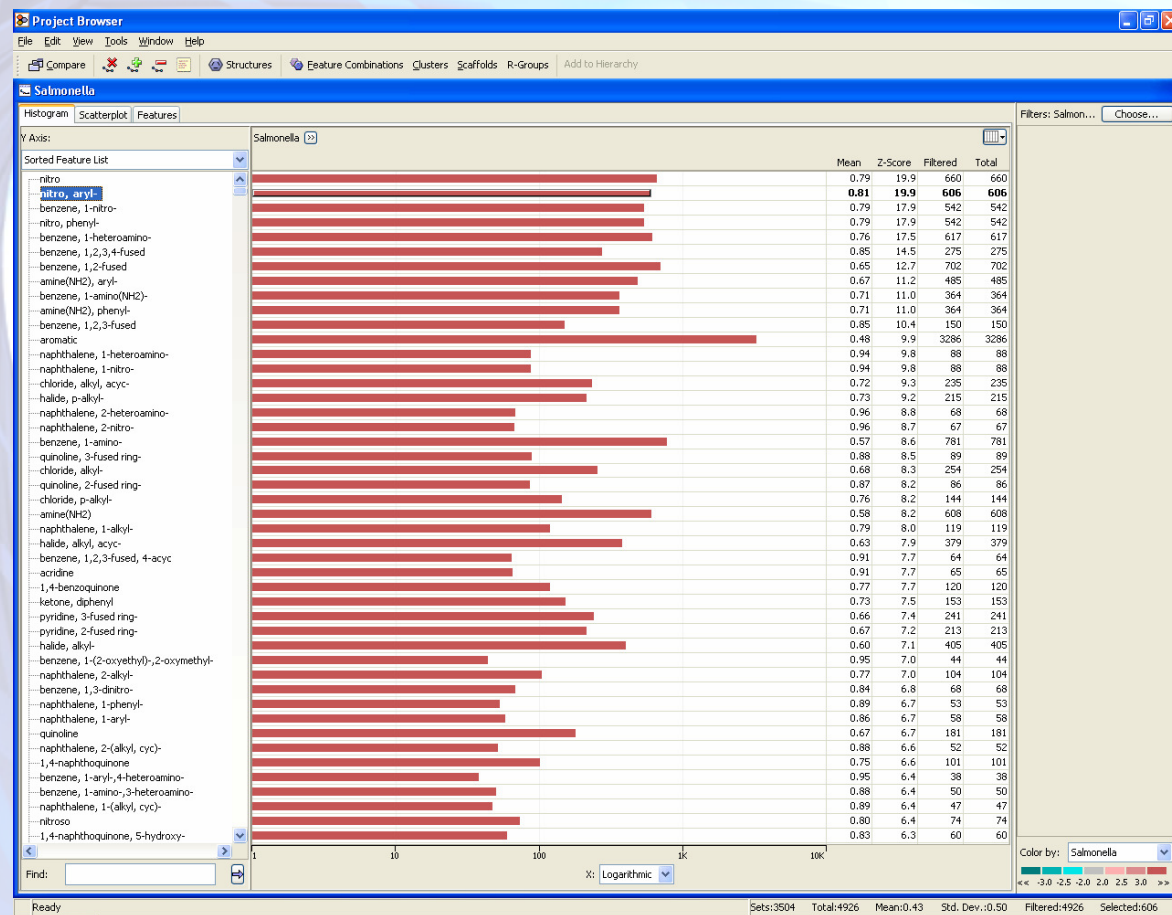
- Tokens encode user identity
- Tokens are valid for a certain time period only (customizable)
- The triplet URI+Action+Token makes up the call to be authorised
- All messages are encrypted (SSL)
- Resource Owners create and modify policies defining access rules

Policies

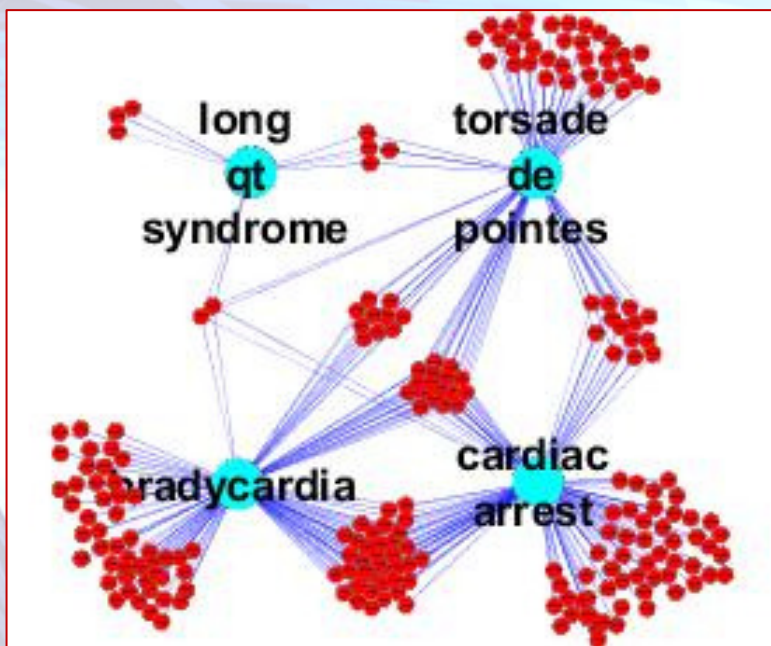


Validation against Confidential Data Case implemented Spring 2011

OpenTox - Leadscope Integration



Analysis of Adverse Events Based on Pharmacological Activity



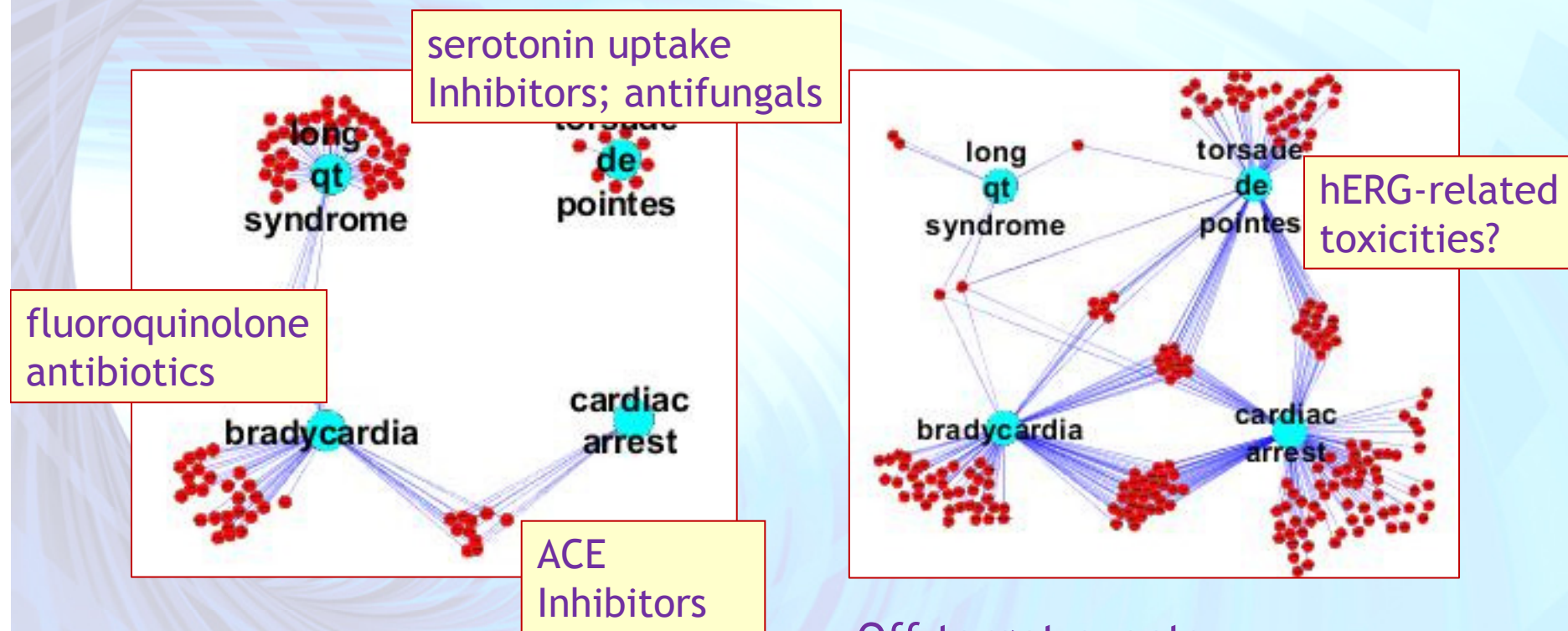
- Cardiac adverse events
- Related to hERG ion channel?

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

REACH and Weight of Evidence

Within the REACH legislation, the so-called Weight of Evidence (WoE) approach is a component of the decision-making procedure on substance properties and thus an important part of the chemical safety assessment. In the legal text the **use of weight of evidence approach is provided for in Annex XI as an option to meet the information requirements of Annexes VII to X.**

According to the ECHA Guidance B the weight of evidence (WoE) approach is not yet a scientifically well-defined term or an agreed formalised concept. It **involves assessing the relevance, reliability and adequacy of each piece of available information, holding the various pieces of information up against each other and reaching a conclusion on the hazard. This process always involves expert judgement. It is important to document and communicate how the evidence-based approach was used in a reliable, robust and transparent manner.**

REACH and Weight of Evidence

The ECHA Practical Guide 2 “How to report weight of evidence” (ECHA PG2) defines WoE as 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 formalized 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.’**

REACH and Weight of Evidence

Within Weight of evidence is closely linked to *integrated testing/information strategies (ITS)*, in that the available evidence **can help to determine the possible subsequent testing steps**.

The WoE approach may be applied if there is sufficient information from **several independent sources** leading to the conclusion that a substance does or does not have a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion (ECHA Evaluation 2010).

If any of the Annex XI conditions for (Q)SAR for waiver are not met, the **(Q)SAR results cannot be used instead of testing but they may be used as a part of a Weight of Evidence approach**.

When data from a single secondary source is used, it is essential to provide further supporting evidence e.g. QSAR predictions, manufacturing data, data taken from material safety data sheets, etc. All relevant information for the hazard endpoint should be addressed and a justified weight should be assigned to it in the overall assessment. (ECHA Evaluation 2010)

Proposed Paper (s): Satisfying REACH Alternative Testing Information 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 (REACH and WoE could be a focus paper itself)
- 6 Predicting Metabolites
- 7 Achieving Harmonisation through Ontologies

Preparation Timeframe Sept-Nov 2011.

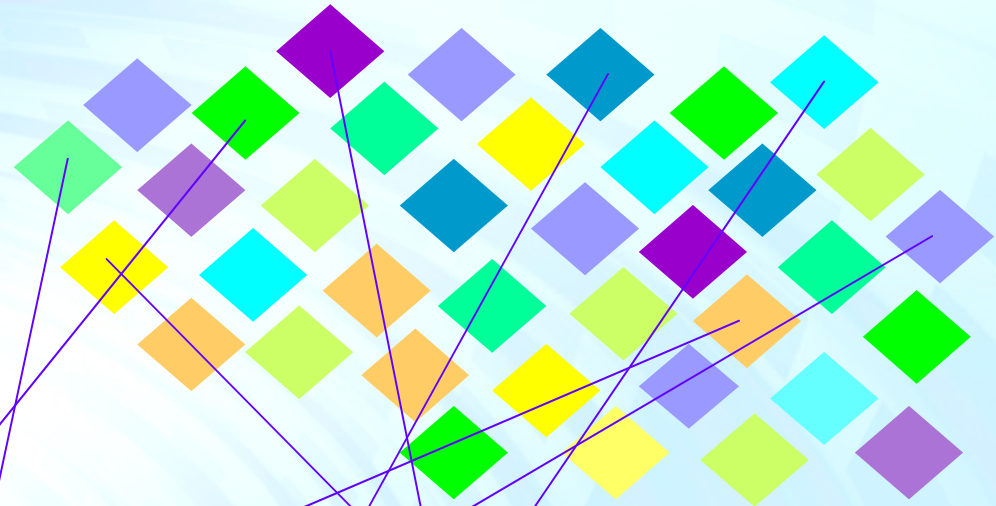
Interested in Collaborating on this paper?

Creation of VO from Collaboration Pool

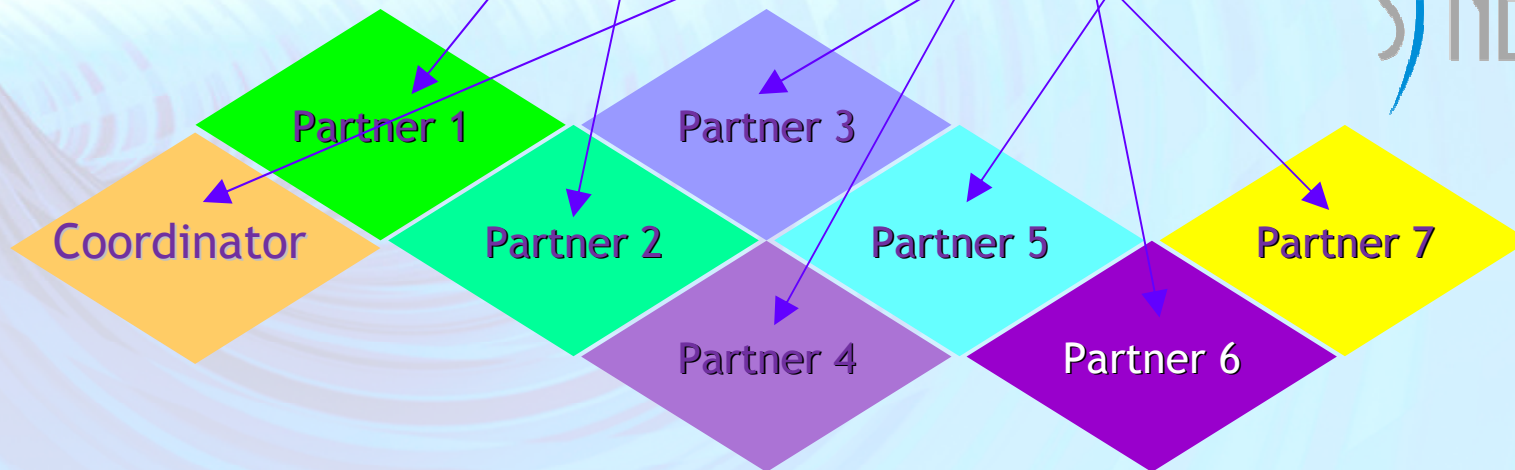
Network

Opportunity

Call for Tender
Need for joint effort
Major project



Virtual Organisation



SYNERGY

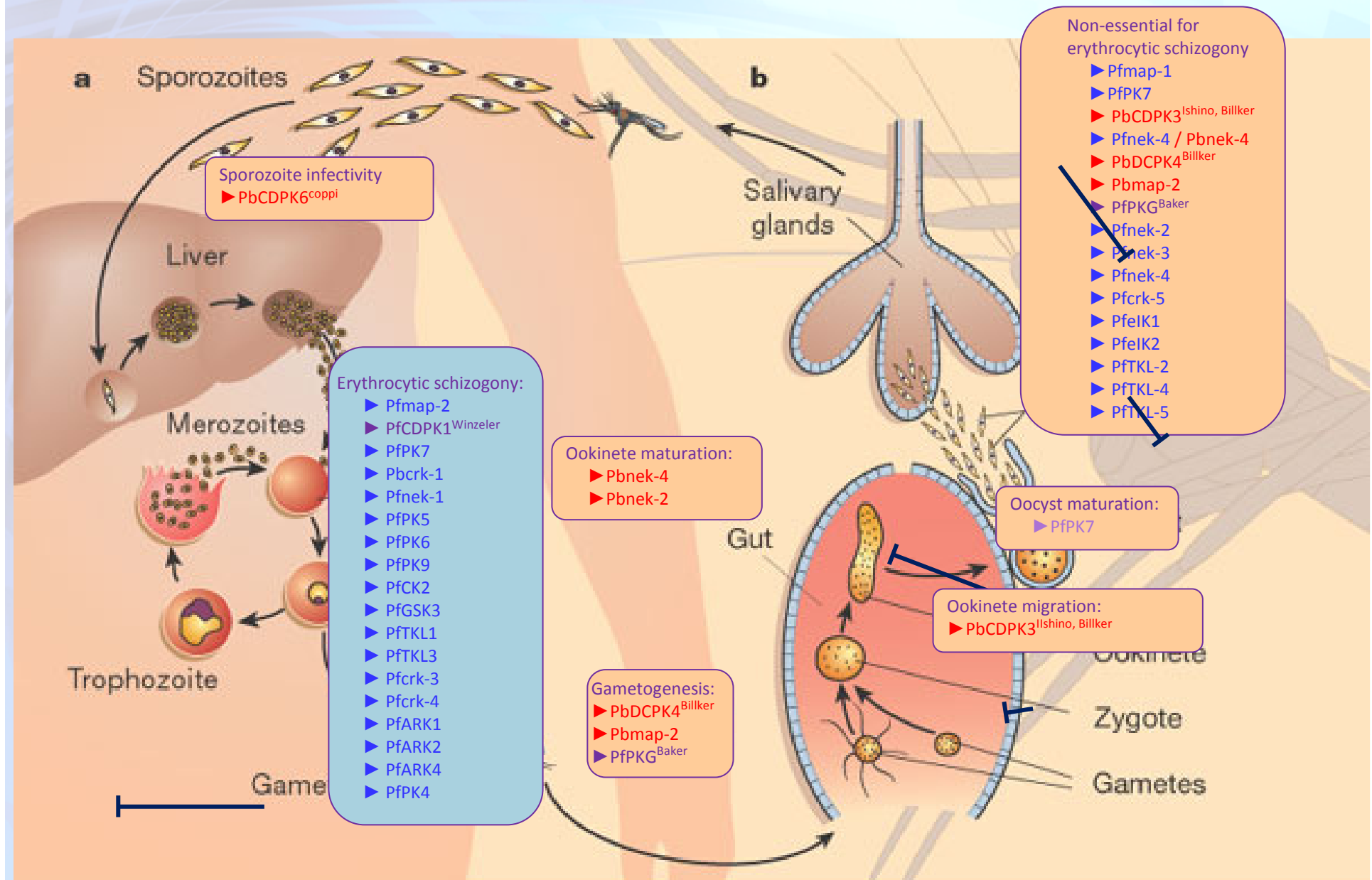
Initial Experience on SAM VO

Scientists Against Malaria (Pilot initiated June 2010)

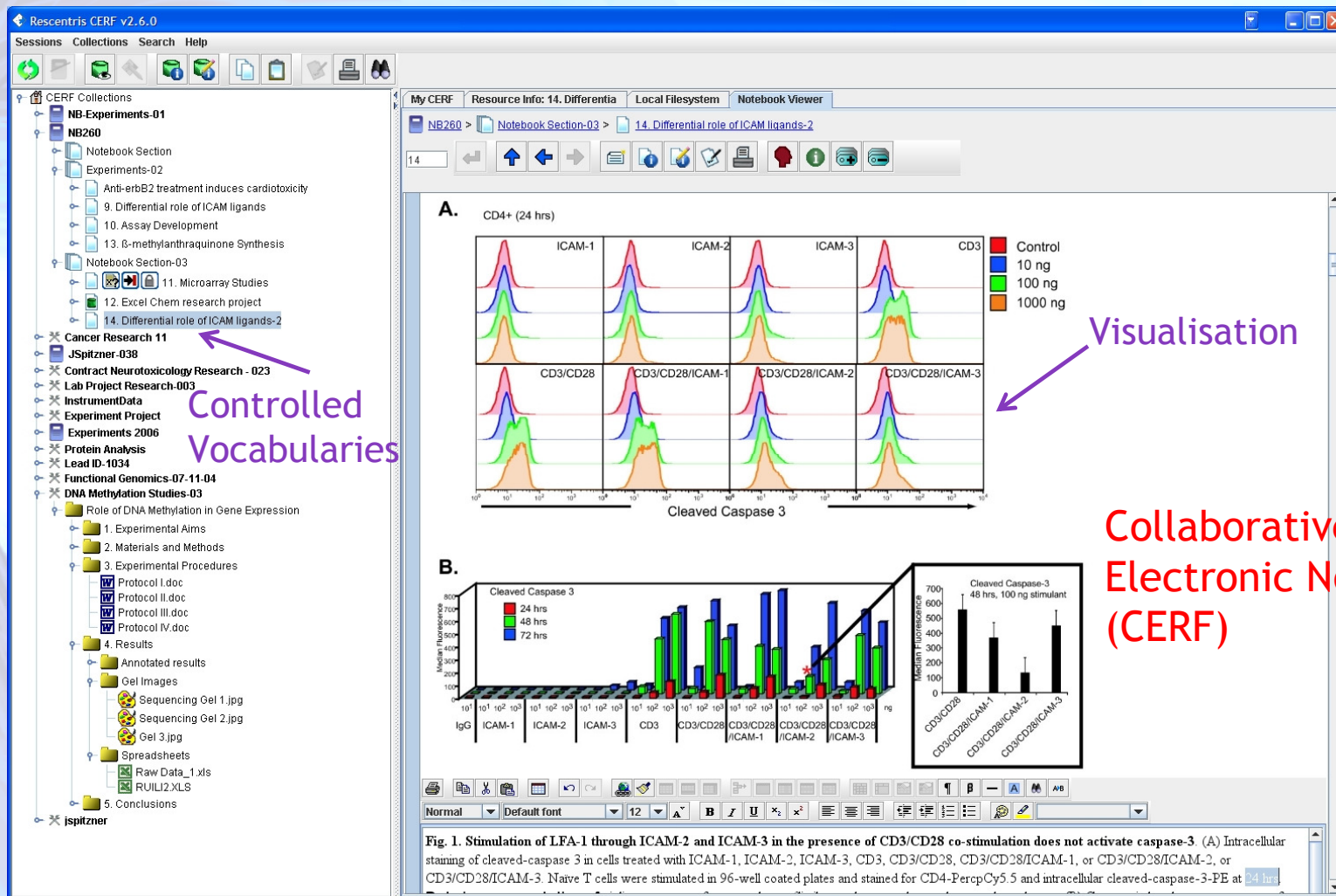
Using a low budget approach, strong interdisciplinary collaboration and innovative infrastructure and modelling developments, we moved a green field drug discovery project on a novel parasitic kinase target with no initial solved structure or known ligand at the start of the Pilot Project to Dose Response characterised leads within 9 months.

We are now extending chemical and kinome space exploration of activity relationships and developing schemes for toxicity profiling and prioritisation of compound libraries.

SAM Virtual Organisation targeting Plasmodium Kinases (www.ScientistsAgainstMalaria.net)



Collaborative Research Framework Integration



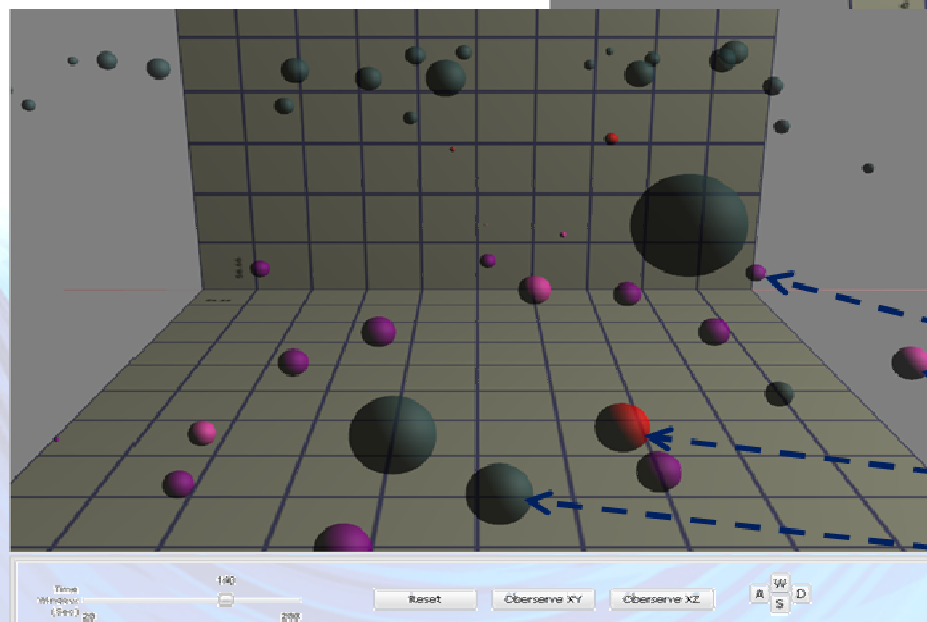
Event Driven Collaboration Architecture







OpenToxLink ICT Architecture



Processing Complex Events Stream

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



Reset	Observe XY	Observe XZ	
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	Phone	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		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

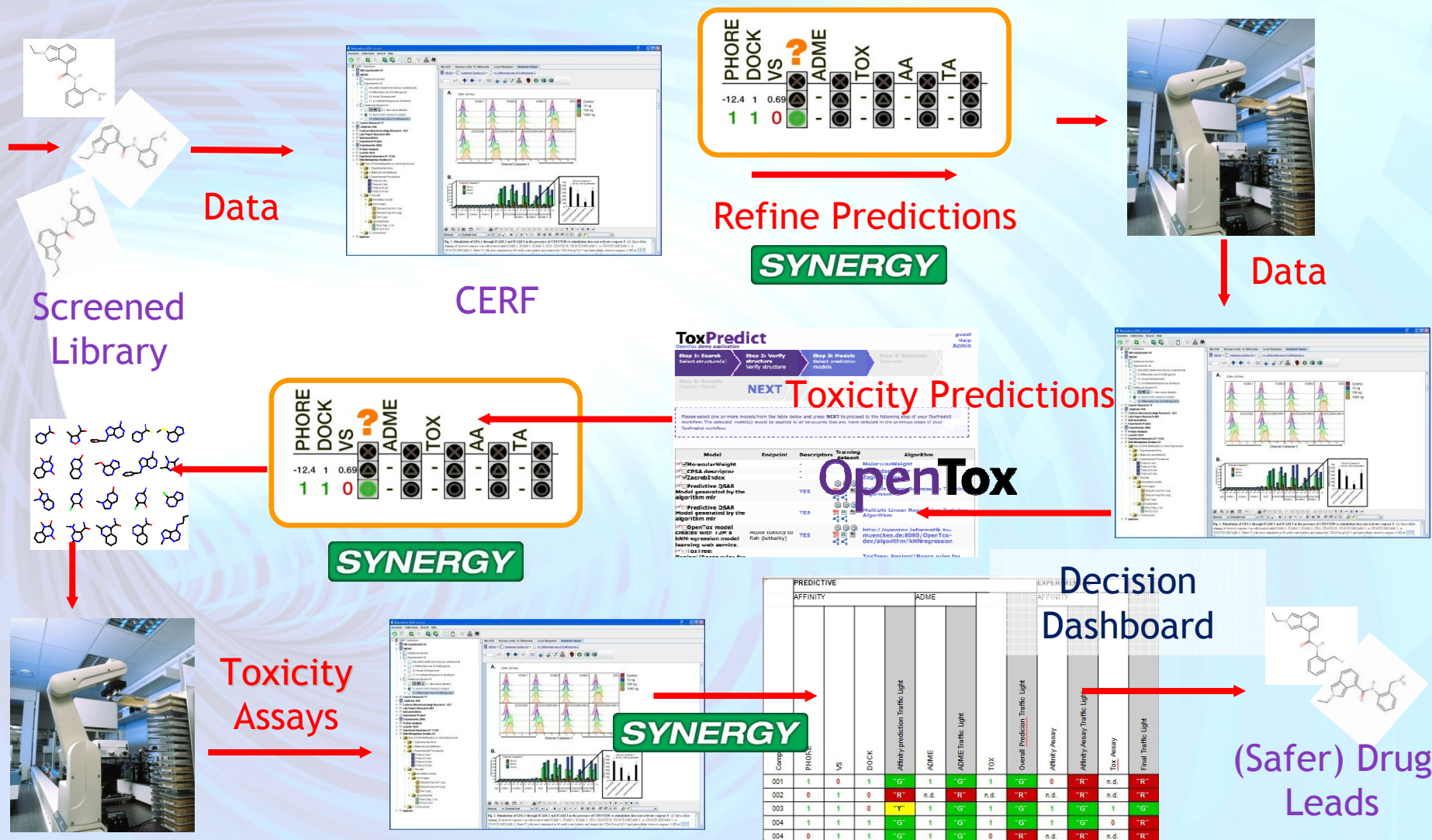
Last Update: Oct 21, 2010 2:57:10 PM

Contributor: Jeff Spitzner

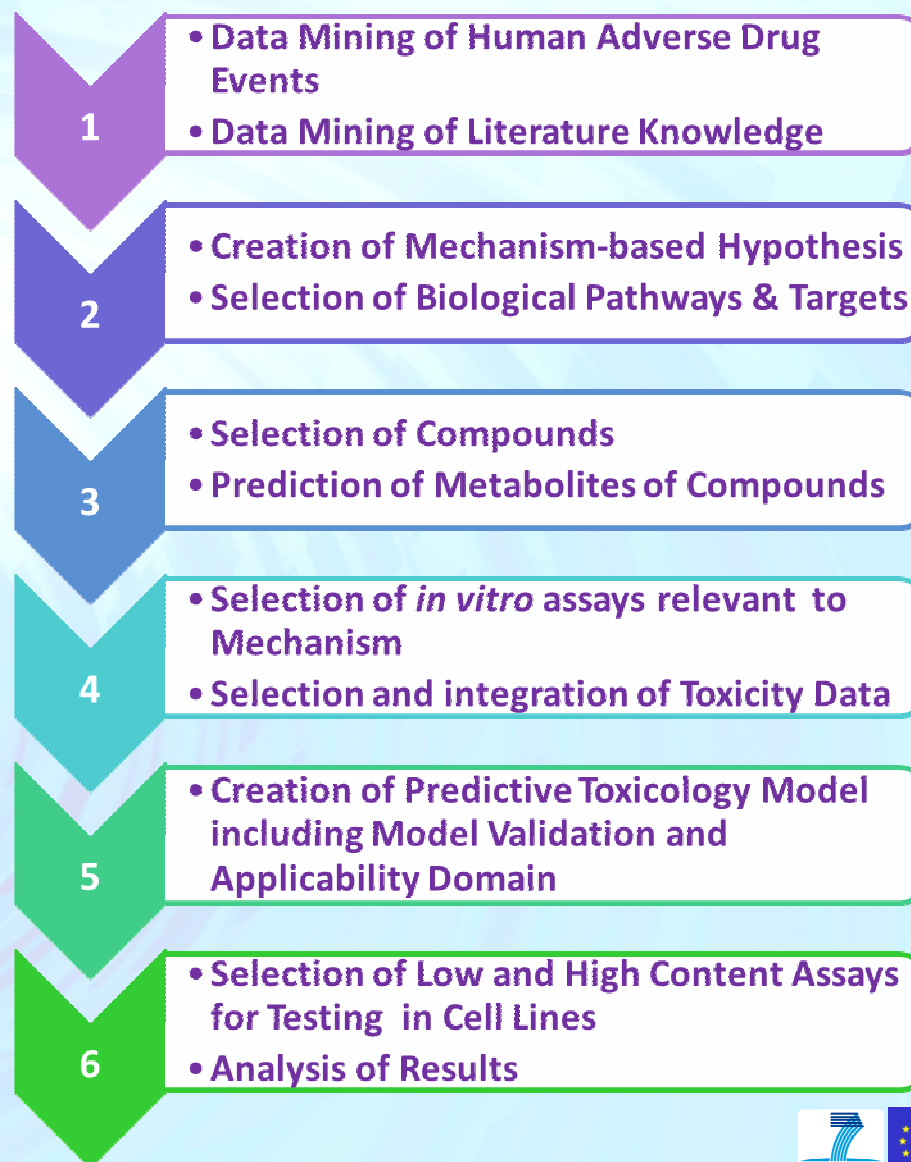
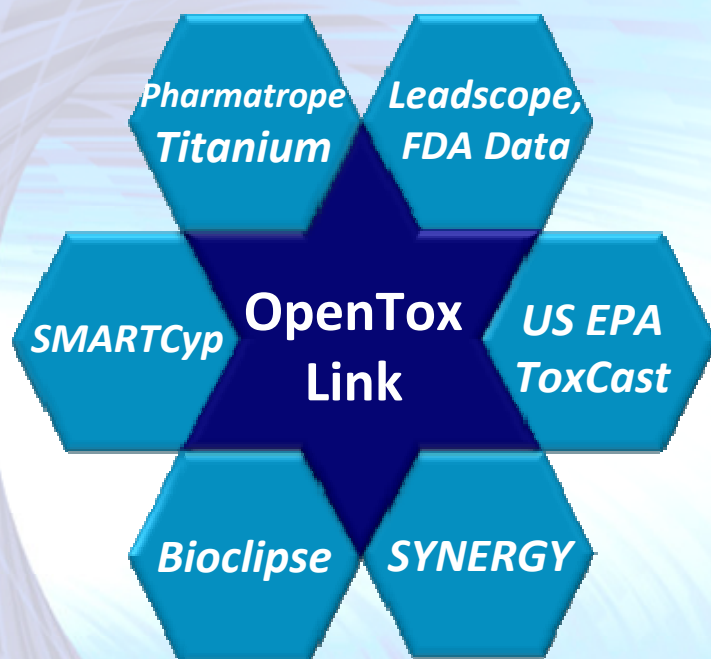
Relations and Annotations ?

Comment Tag Browse Tags

Synergy Drug Design Collaboration Pilot



The OpenToxLink Virtual Organisation



Weight of Evidence driven Prioritisation

A Weight-of-Evidence Approach to Prioritisation based on Consensus across Multiple Sources of Information

Roman Affentranger and Barry Hardy, Douglas Connect, Switzerland

Glenn Myatt, Leadscope, USA

Nina Jeliaskova, IdeaConsult, Bulgaria

Matthew Clark and Jeff Wiseman, Pharmatropo, USA

We present the results of initial work carried out within the OpenToxLink Virtual Organization, applying a Weight-of-Evidence (WoE) approach based on consensus across multiple sources of information for the prediction of adverse effects of a large set of potential antimalarial compounds. The work was carried out as part of the EU FP7 project SYNERGY, evaluating the support of decision dashboards and event-driven collaborative research of software developed within SYNERGY. ...

Poster presented at OpenTox 2011, Munich

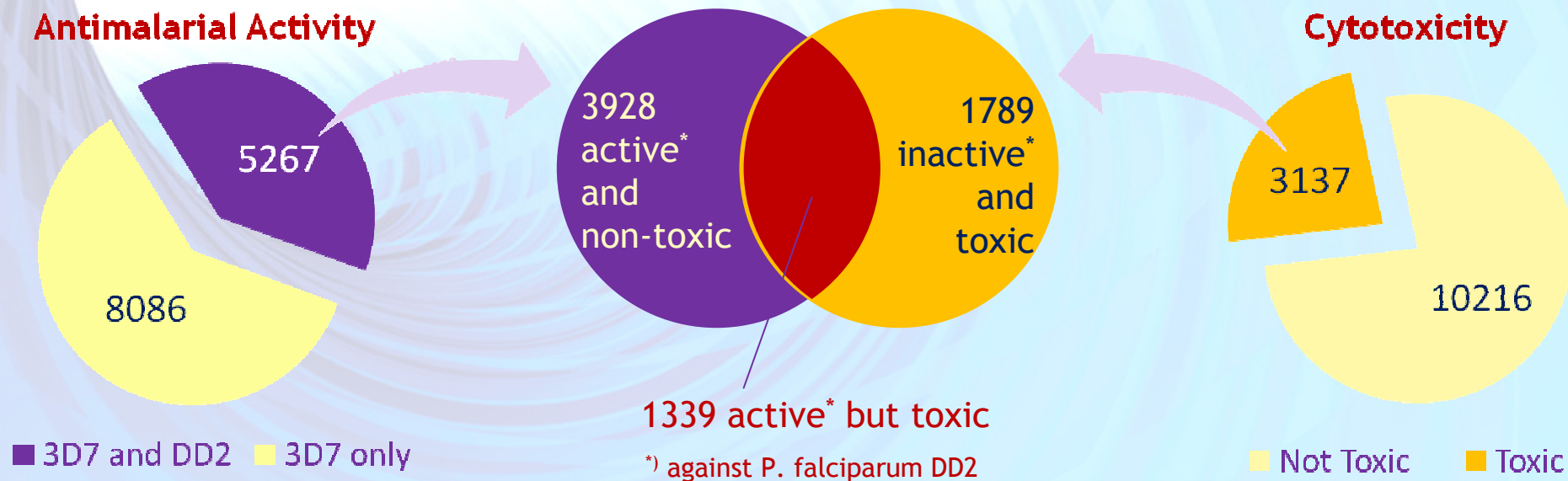
www.opentox.org/meet/opentox2011/posters/a-weight-of-evidence-approach-to-prioritisation-based-on-consensus-across-multiple-sources-of-information

The TCAMS MalariaBox

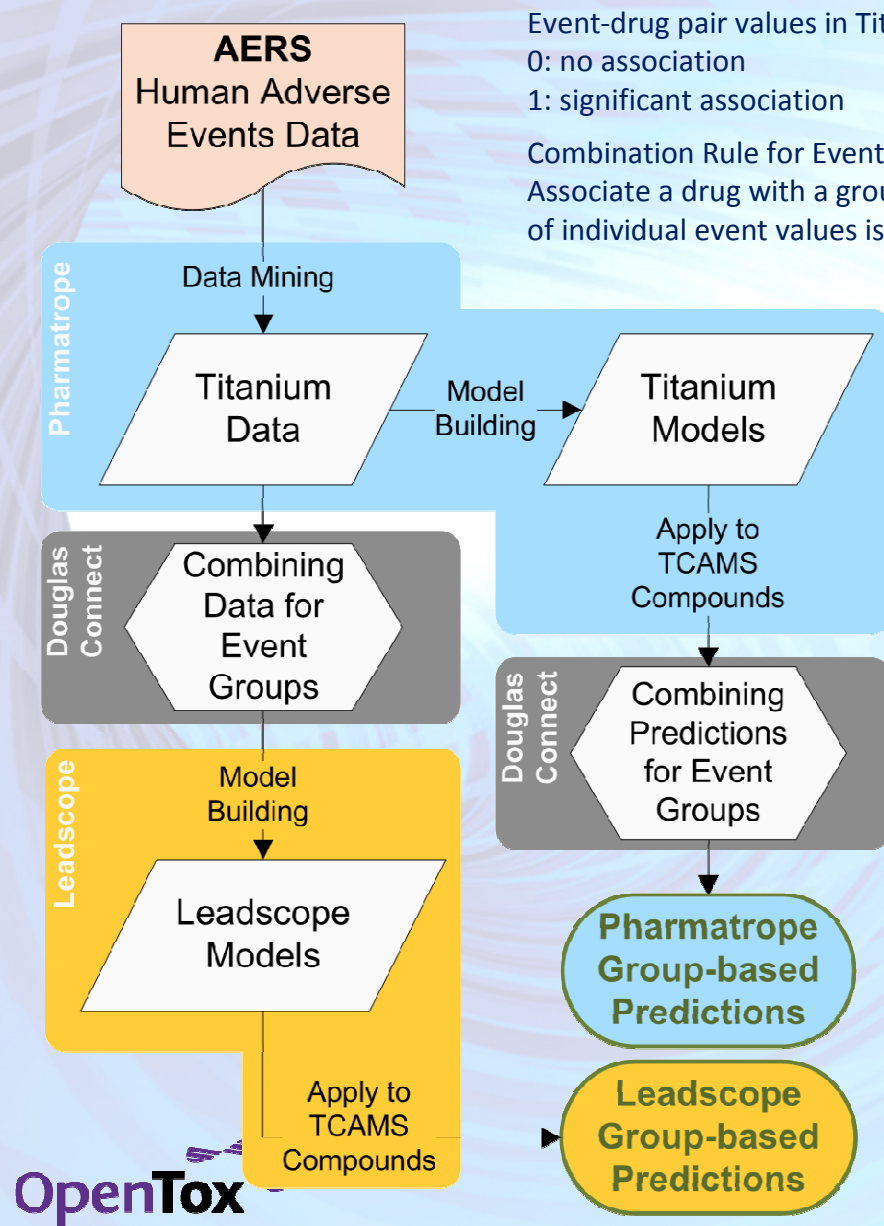
“Malaria Box”: A collection of chemical compounds active against (i.e. inhibiting growth of) the malaria parasite *Plasmodium falciparum*

Data provided that is relevant for this project:

- Activity against (growth inhibition of) *P. falciparum* strain 3D7 (common strain)
- Activity against (growth inhibition of) *P. falciparum* strain DD2 (multi-drug resistant strain)
- Cytotoxicity against (growth inhibition of) human hepatocytes, HepG2 (hepatoma cells)



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)

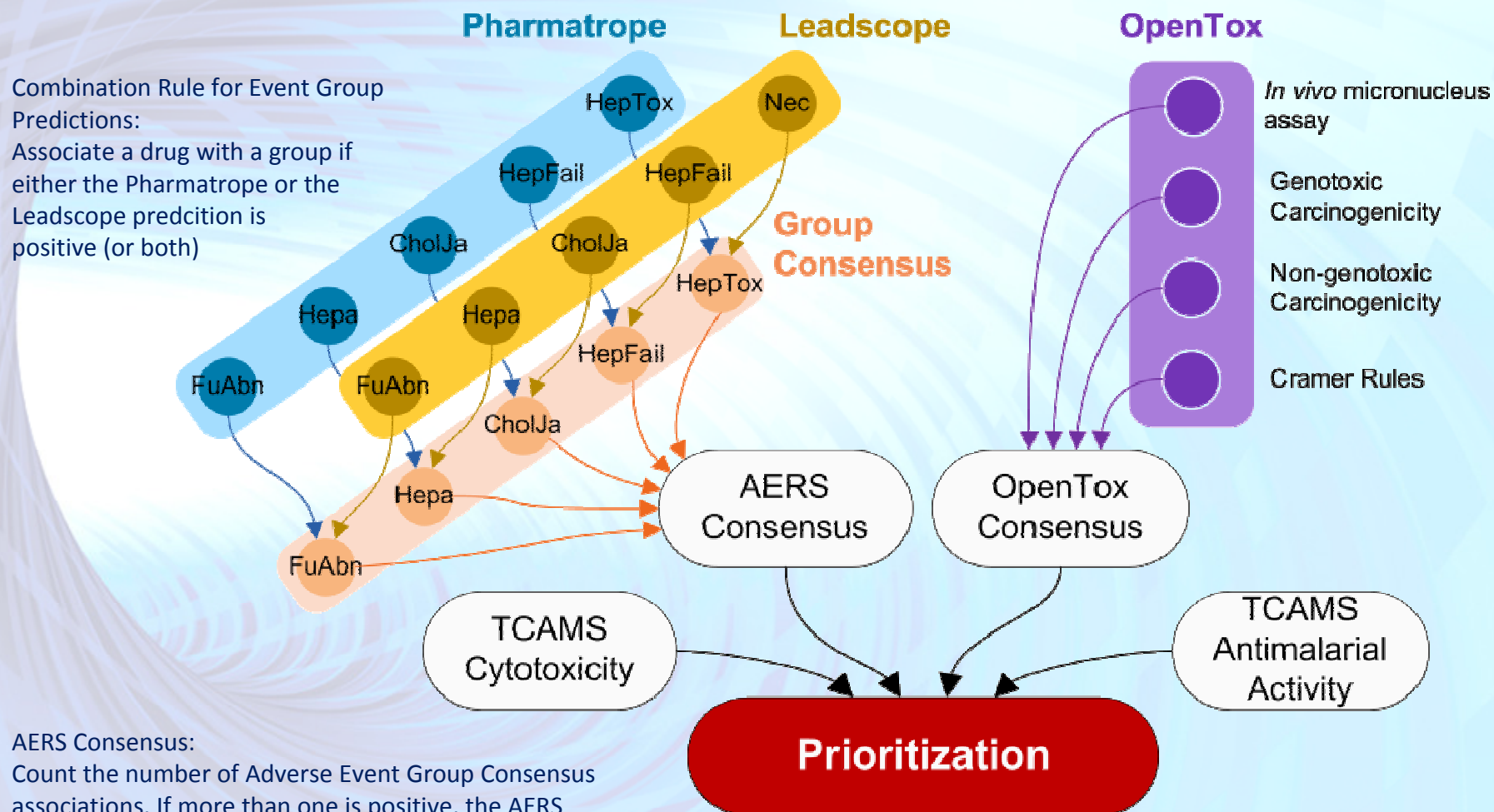
Combination Rule for Event Groups:

Associate a drug with a group if the sum of individual event values is larger or equal to 0.4.

Adverse Event Groups

Adverse Event Groups	Group Name
Hepatic function abnormal Liver disorder	FuAbn
Hepatic necrosis	Nec
Cytolytic hepatitis Hepatitis Hepatitis acute Hepatitis toxic	Hepa
Cholestasis Jaundice Hepatitis cholestatic jaundice cholestatic Yellow skin	CholJa
Hepatic failure Hepatitis fulminant Acute hepatic failure Hepatorenal failure	HepFail
Hepatotoxicity Hepatomegaly Hyperbilirubinaemia Hepatosplenomegaly	HepTox

Combining Predictions and Experimental Data



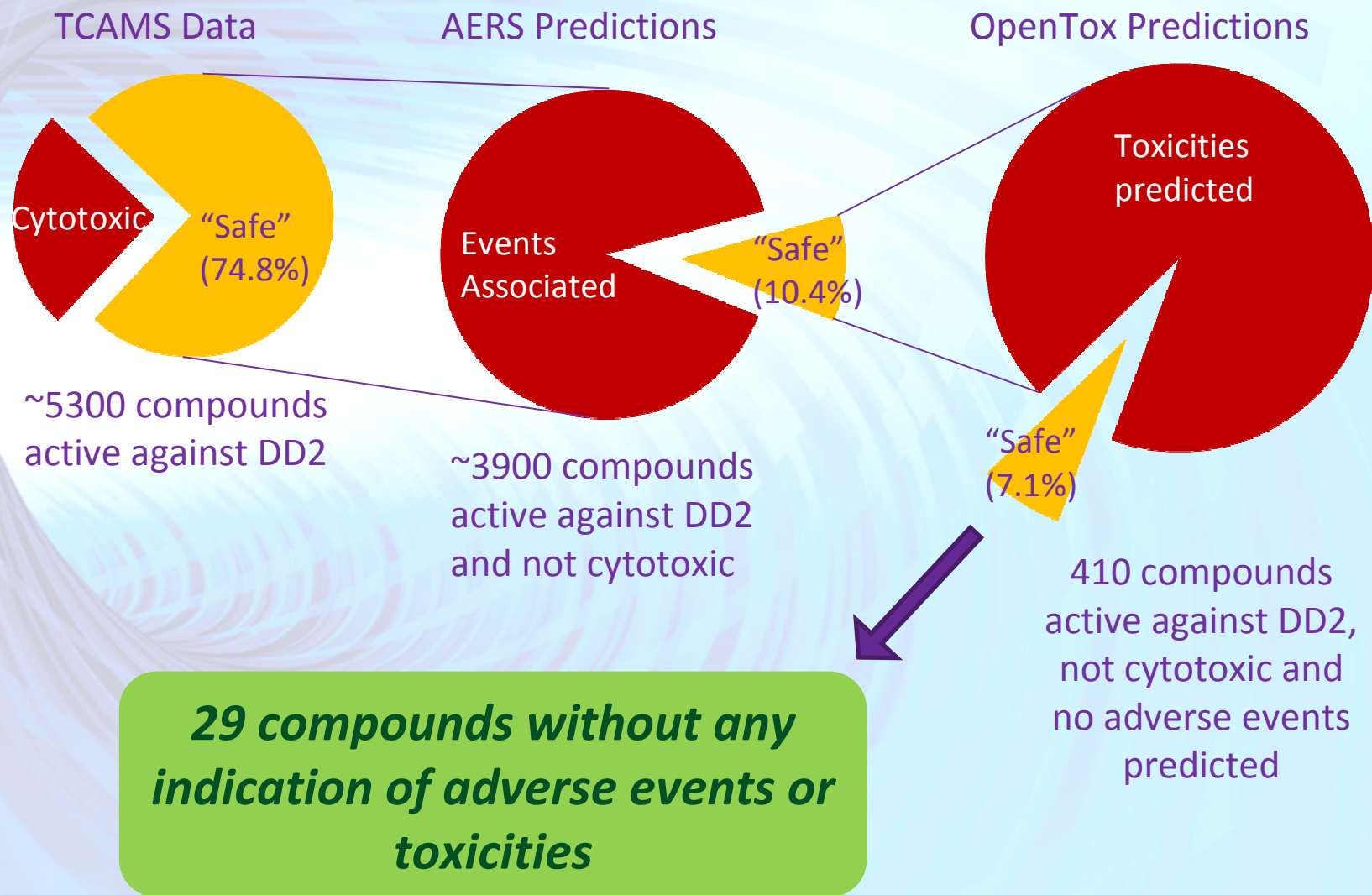
AERS Consensus:
Count the number of Adverse Event Group Consensus associations. If more than one is positive, the AERS Consensus is positive.

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 μ M.

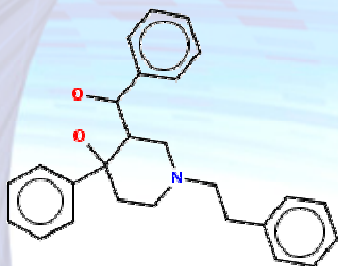
TCAMS Antimalarial Activity:
Positive if > 80% growth inhibition of *P. Falciparum* DD2 at 2 μ M.

Compound Prioritization Results



Example compounds

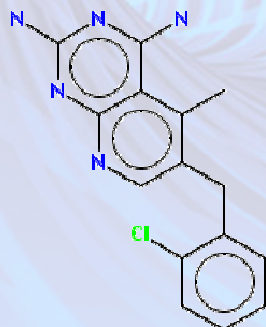
"Safe"



TCMDC-131287:

- No predicted association with adverse events (consistent)
- Negative for carcinogenicity and mutagenicity
- No inhibition of HepG2 growth
- Strong inhibition of *P. falciparum* DD2 growth

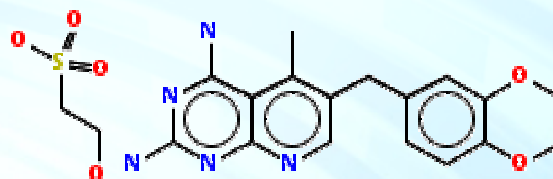
"Toxic"



TCMDC-137245:

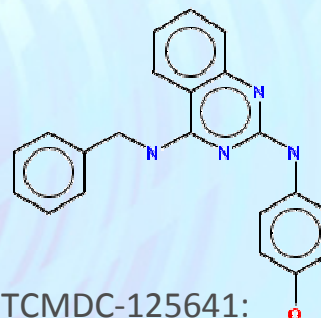
- Associated with 4 and 5 (out of 5) adverse events group by Pharmatropé and Leadscope, respectively
- Positive for carcinogenicity and mutagenicity, Cramer Class III
- 67% HepG2 inhibition (10 μ M)
- 91% *P. falciparum* DD2 growth inhibition (at 2 μ M)

Ambiguous, Further Data Required



TCMDC-138057:

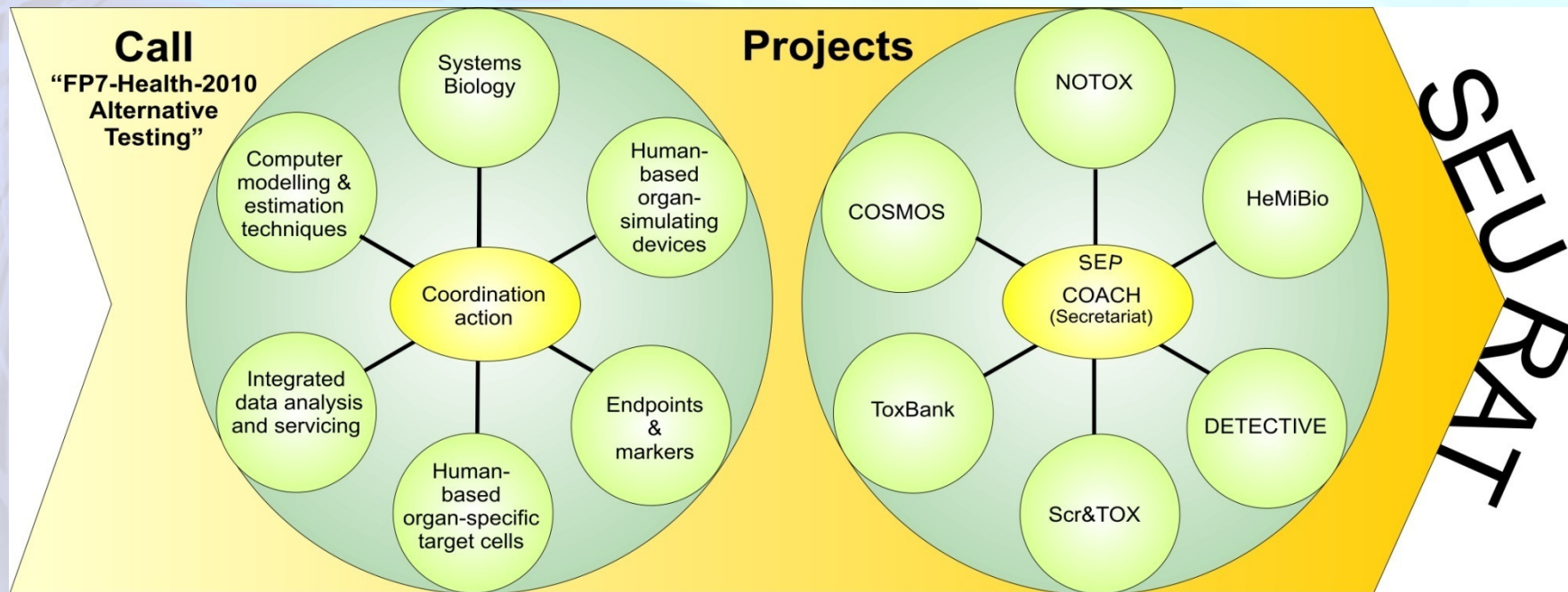
- Predicted association with many adverse events groups
- Positive for carcinogenicity and mutagenicity
- Considered safe (Class I) with Cramer rules
- Inhibition of HepG2 growth could not be measured
- Strong inhibition of *P. falciparum* DD2 growth



TCMDC-125641:

- No adverse event association predicted with Pharmatropé models
- Strong association with all five adverse events groups predicted with the Leadscope models
- Negative for carcinogenicity and mutagenicity
- Intermediate inhibition of HepG2 growth (33% at 10 μ M)
- Strong inhibition of *P. falciparum* DD2 growth (100% at 2 μ M)

The Building Blocks of SEURAT- 1



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

The Building Blocks of SEURAT-1



- Stem cell differentiation for providing human-based organ specific target cells



- Development of a hepatic microfluidic bioreactor



- Identification and investigation of human biomarkers



- Delivery of computational tools to predict the effects of chemicals based on *in silico* calculations and estimation techniques



- Development of systems biological tools for organotypic human cell cultures



- Supporting integrated data analysis and servicing of alternative testing methods in toxicology

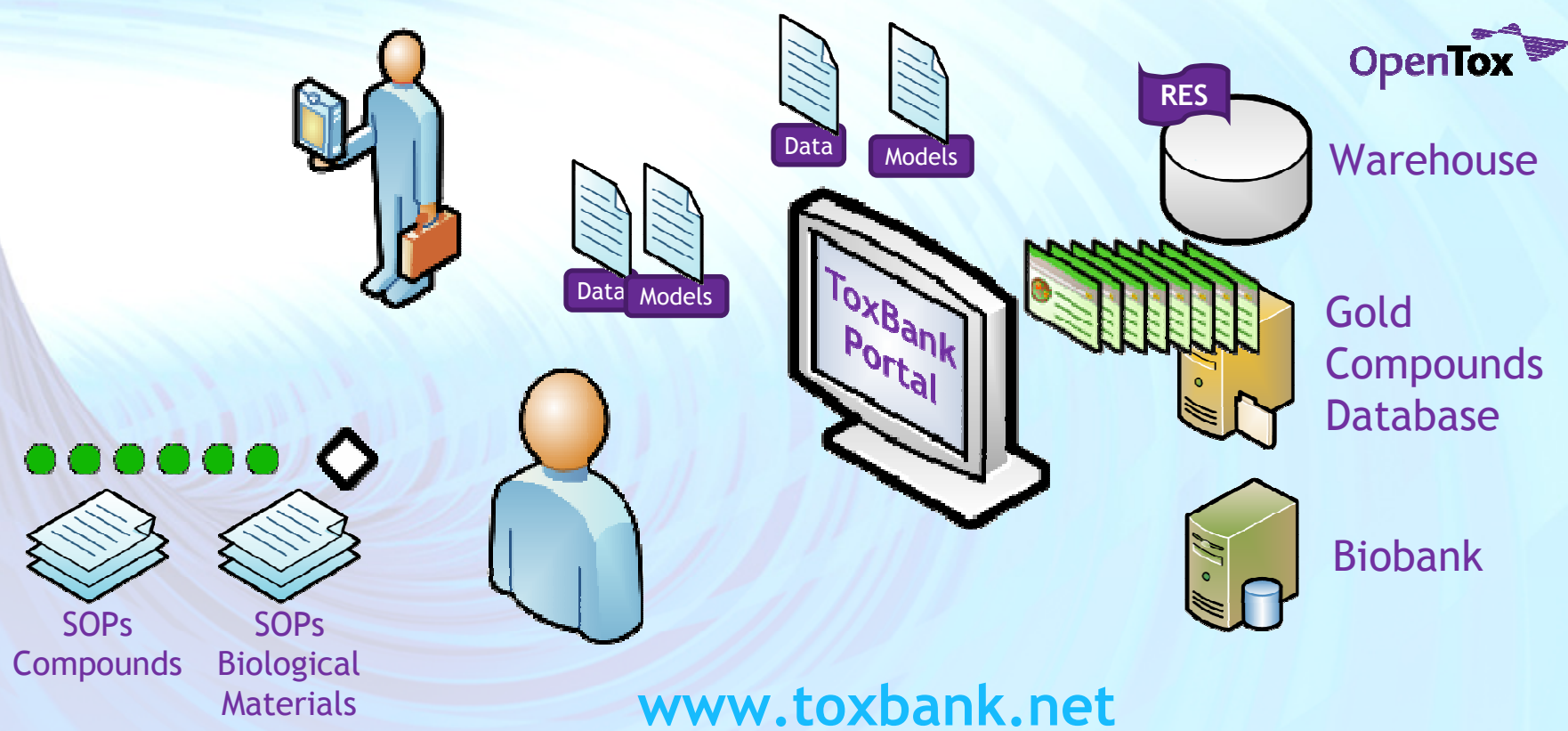


- Cluster level Coordinating and Support Action



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



This project will be jointly funded by COLIPA and the EC. Any opinions expressed in this slide are those of the author. COLIPA is not liable for any use that may be made of the information contained therein.

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

There will be an OpenTox 2012!



Collaborating Partners

In Silico Toxicology,
Switzerland

Douglas Connect,
Switzerland
(Coordinator)

Albert Ludwigs University
Freiburg, Germany

Ideaconsult,
Bulgaria

Istituto Superiore
di Sanità, Italy

Technical University
of Munich, 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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For more information, visit

www.opentox.org

Contact:

[barry.hardy -\(at\)- douglasconnect.com](mailto:barry.hardy-(at)-douglasconnect.com)

twitter.com/barryhardy

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