OpenTox:
An open source web service platform for toxicity prediction

ACS, Anaheim, 30th March 2011

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***Co-Presenters**

OpenTox

SEVENTH FRAMEWORK PROGRAMME

Abstract

The new European Union (EU) REACH chemical legislation will require over 9 million additional test animals, if no alternative methods for toxicity prediction are accepted. However, the number of test animals could be significantly reduced by utilizing existing experimental data in conjunction with (Quantitative) Structure Activity Relationship ((Q)SAR) models.

To address the challenge, the European Commission has funded the OpenTox (www.OpenTox.org) project to develop an open source web-service-based framework, that provides unified access to experimental toxicity data, *in Silico* models (including (Q)SAR), and validation/reporting procedures.

Now, in the final year of the initial three-year project, the current state of architecture, Open API, algorithms, ontologies, and approach to web services are presented. Our experiences on current collaborative approaches aiming to combine OpenTox with other systems such as CERF, Bioclipse, CDK, and SYNERGY to create “superinteroperable K-infrastructure” are discussed both in terms of conceptual promise and implementation reality.

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Topics

- **New EU legislation "REACH"** *David Gallagher*
- **The chemistry challenges**
- **Prototype applications (Tox prediction)**
- **User Needs** *Sunil Chawla*
- **Semantic Web for Predictive Toxicology**
- **Key Components**
- **Web Service Interoperability**
- **Achievements**

Barry Hardy (P.I.)

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Background - REACH

“Registration, Evaluation, Authorisation & Restriction of Chemicals”

European Union Legislation, 2007

All chemicals imported or manufactured in Europe must be registered

from 1st December 2010 (European Chemicals Agency - ECHA)

“…protecting human health and the environment…” Geert Dancet, ECHA

Responsibility:

Manufacturers and importers to

provide safety information & manage risks

Threshold:

Phased:	**2010**	**> 1,000 tons p.a.**
	2018	**> 1 ton p.a.**

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Impact of REACH

Registration per chemical: $2M to $14M[2]

IUCLID: International Uniform Chemical Information Database

Registration submitted by 22 Nov. 2010: 19,237[1]
Chemicals pre-registered by 1 Dec. 2008: **143,000[2]**

54M[3] - 9M[4] additional test animals

"...promote alternative methods for assessing hazards of substances.....animal testing as a last resort..." Geert Dancet, ECHA

1. C&EN, Nov 29, 2010, P. 15
2. en.wikipedia.org/wiki/Registration, Evaluation, Authorisation and Restriction of Chemicals
3. T. Hartung & C. Rovida: Chemical regulators have overreached. Opinion in Nature, vol. 460, 27 Aug '09.
4. ECHA - New study inaccurate on the number of test animals for REACH. Helsinki, 28 August 2009

Funding

European Union
Seventh Framework Programme

Program: HEALTH-2007-1.3-3

Promotion, development, validation, acceptance and implementation of QSARs for toxicology

Project Reference Number Health-F5-2008-200787.

ca. $4M (2008 - 2011)

Awarded to: **OpenTox Consortium**

Proposal: “An Open Source Predictive Toxicology Framework”

www.opentox.org

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OpenTox Partners

Douglas Connect, Switzerland (P.I.)

In Silico Toxicology, Switzerland

Ideaconsult, Bulgaria

David Gallagher, UK

Seascape Learning & JNU, India

Superior Health Institute (ISS), Italy

Technical University of Munich, Germany

Albert Ludwigs University Freiburg, Germany

Fraunhofer Institute for Toxicology & Experimental Medicine, Germany

Institute of Biomedical Chem. of the Russian Acad. of Medical Sci., Russia

National Technical University of Athens, Greece

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OpenTox Goals

Development of:

- **an interoperable, extensible predictive toxicology framework**

Containing state-of-the-art:

- **QSARs & SARs**
- **cheminfomatics, bioinfomatics**
- **statistical and data mining tools**
- **computational chemistry & biology algorithms & models**
- ***in vitro* and *in vivo* data resources**
- **ontologies**
- **user interfaces…**

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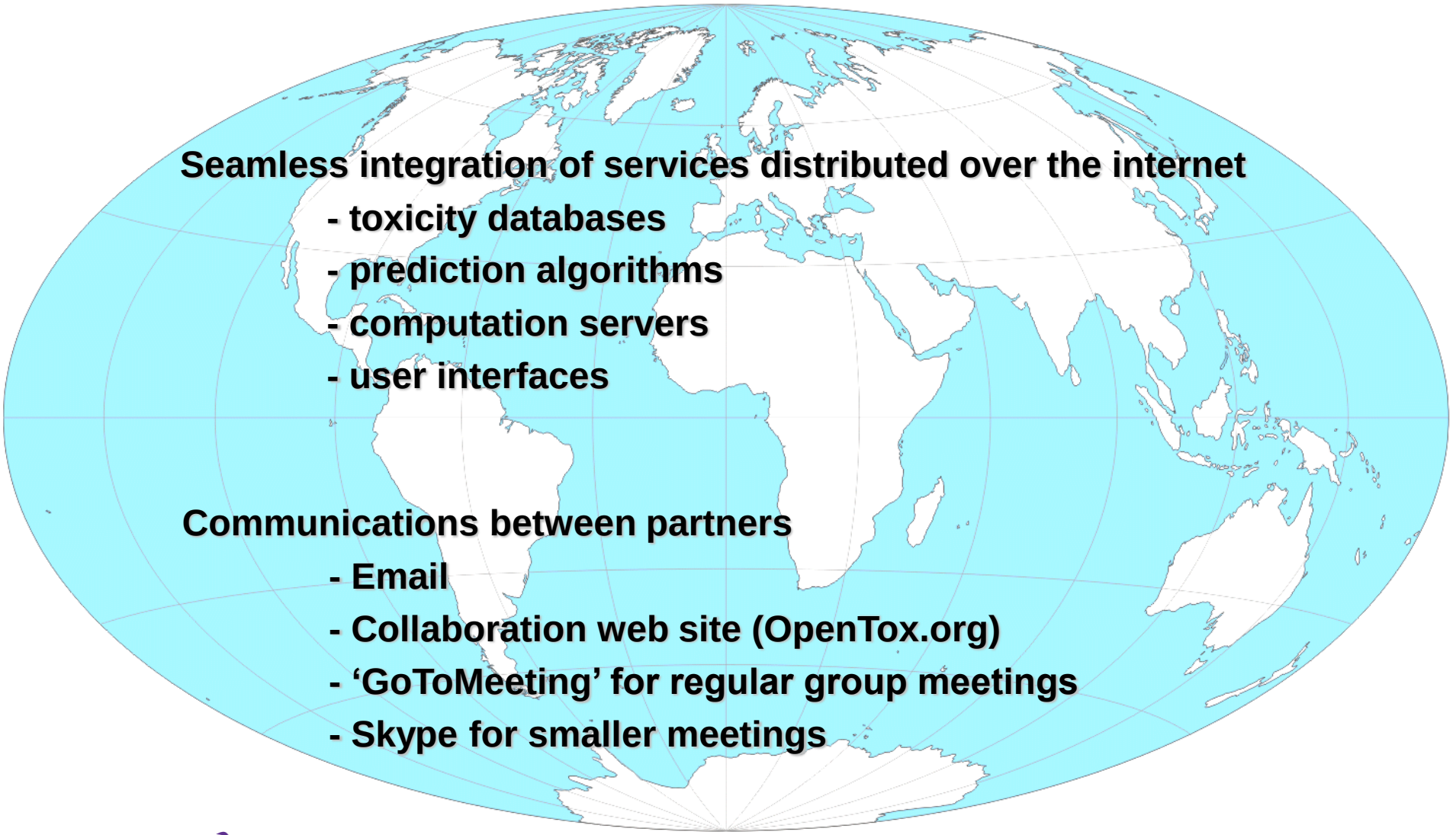
QSAR: Quantitative Structure-Activity Relationships
Ontology: formal definitions and relationships between entities in a domain

OpenTox & “The Internet & Chemistry”



Seamless integration of services distributed over the internet

- toxicity databases
- prediction algorithms
- computation servers
- user interfaces

Communications between partners

- Email
- Collaboration web site (OpenTox.org)
- ‘GoToMeeting’ for regular group meetings
- Skype for smaller meetings

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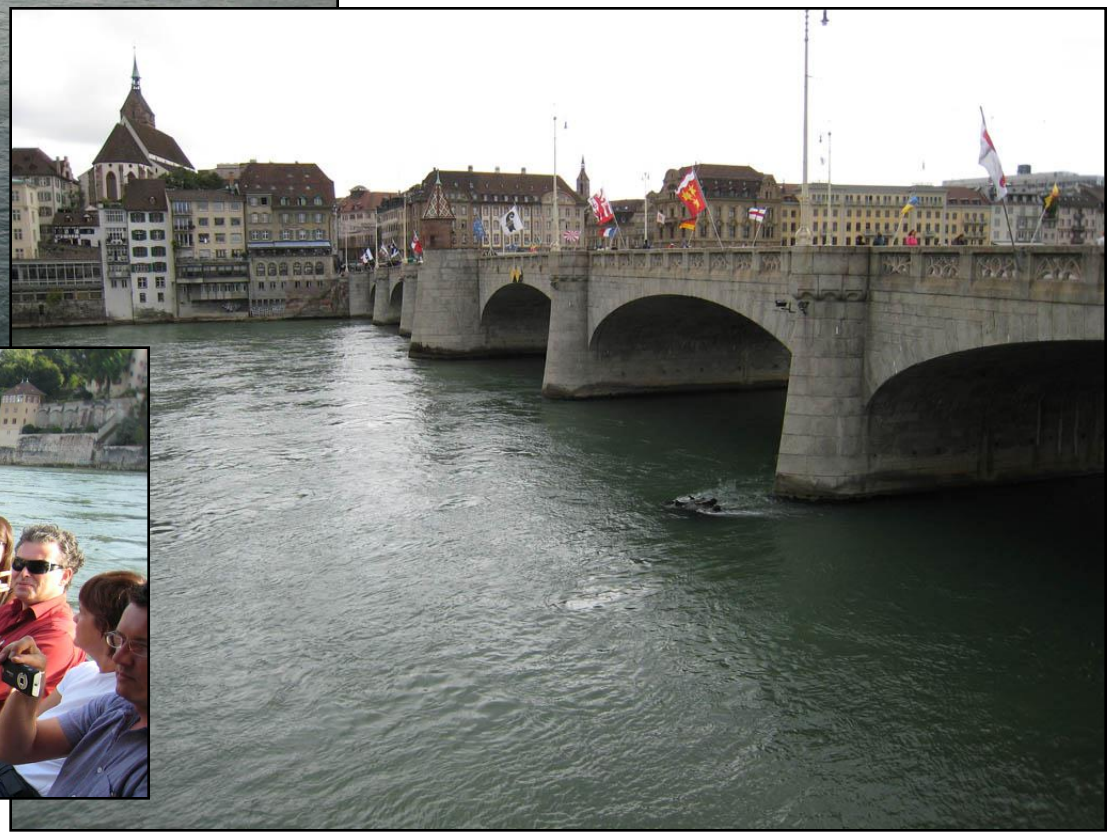
Basel, Switzerland

Sept. 2008

OpenTox kick-off meeting



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SEVENTH FRAMEWORK PROGRAMME

The Challenges

- **QSARs for predicting toxicity**

  (Q)SAR algorithms & descriptors

  consensus predictions

  validation of models

  applicability domains

  transparency

- **Toxicity data**

  standards, quality, licensing, confidentiality

- **Metabolite predictors**

  e.g. *SMARTcyp, CypScore*

- **Retrieval of supporting information**

  database mining, text mining

- **Integrated across the internet**

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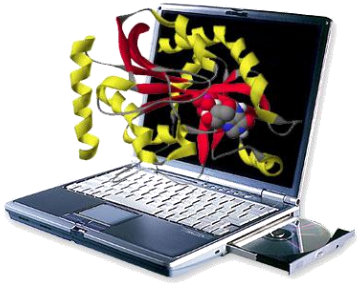
in Silico Methods Considered

(Q)SAR	Quantitative Structure-Activity Relationships
Structural Alerts	(de)activating fragments or functional groups
Read Across	Expert knowledge, compare related chemicals
Database mining	for same or similar chemicals
Text mining	for reports on same or similar chemicals
Third-party packages….	



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Reporting: Validation of Predictions

OECD Guidelines:

1. **Defined endpoint**
   well defined ‘homogeneous’ training data

2. **Unambiguous prediction algorithm**
   fully documented prediction models

3. **Defined applicability domain**
   documented algorithms for chemical space of model

4. **Appropriate measures of goodness-of-fit, robustness, & predictivity**
   scientifically sound: r^2, CVr^2, RMSE, skew, confusion matrix, etc.

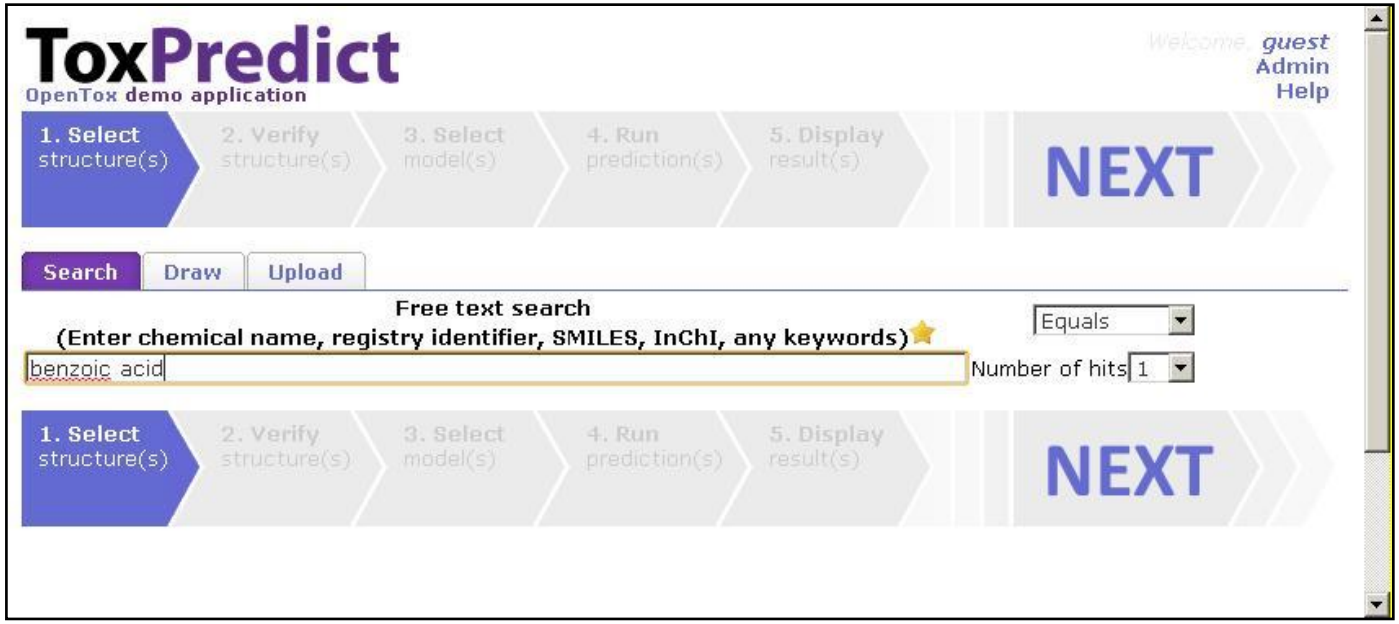
5. **Mechanistic interpretation, if possible**
   key descriptors, human evaluation, can improve confidence

Prototype Application 1: ToxPredict

ToxPredict (www.toxpredict.org)

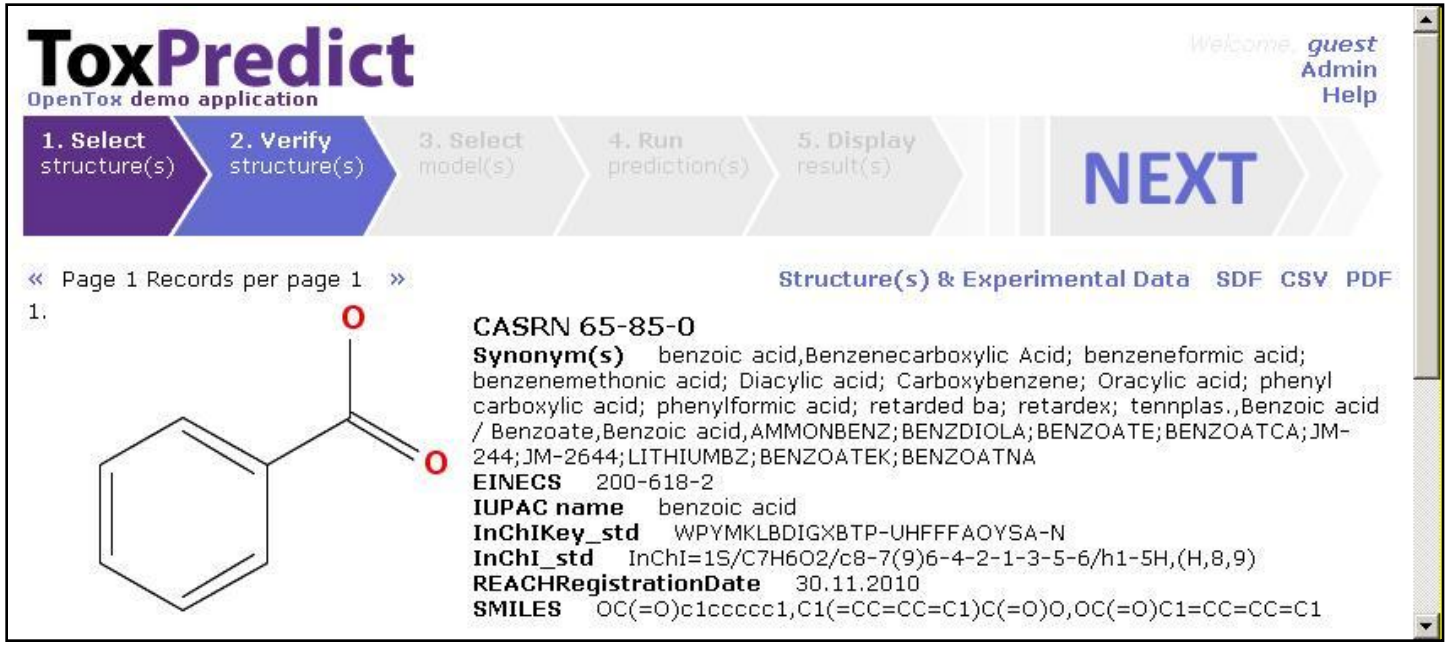
Browser-based GUI enables non-computational experts to enter a single structure and get a toxicity report back based on available end-points (currently 18)

Step 1, Enter the compound



ToxPredict (2)

Step 2: Verify structure and description



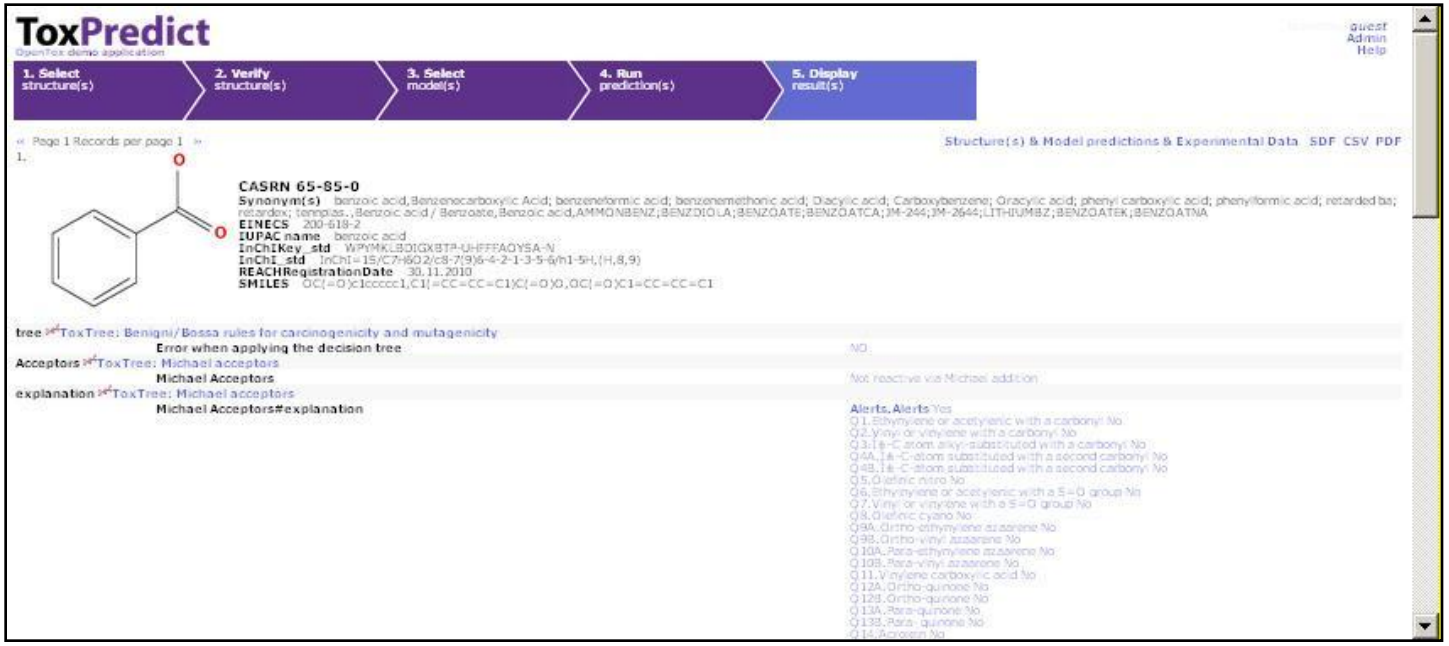
ToxPredict (3)

Step 3: Select toxicity models

Run calculations

ToxPredict (4)

Step 4: View predictions & validation reports



www.ToxPredict.org

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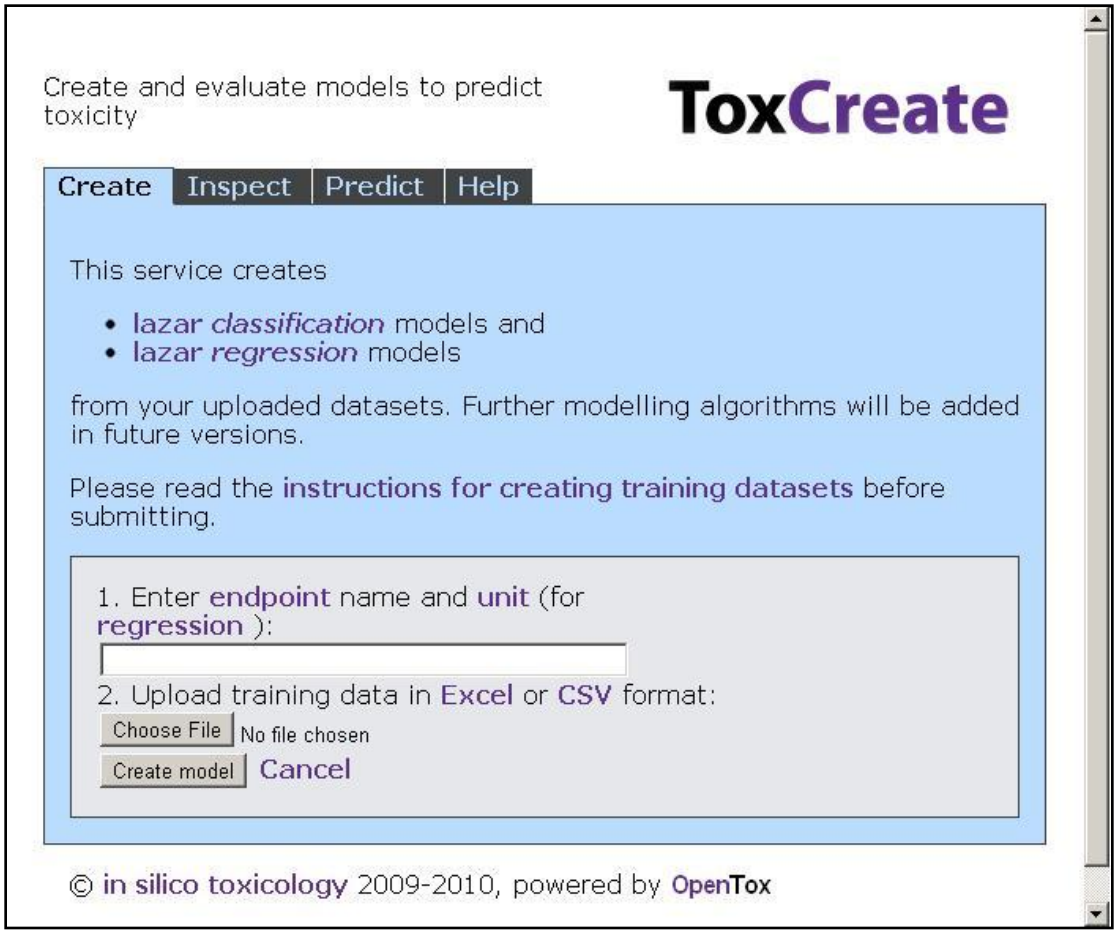
Prototype Application 2: ToxCreate

Creates a model from a training set (www.toxcreate.org)

Step 1, upload training set, and create model



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ToxCreate (2)

Step 2, View prediction model & validation report

hampster test2

Status:	Completed
Started:	03/02/2011 - 03:00:18AM
Training compounds:	85
Warnings:	-
Algorithm:	lazar
Type:	classification
Descriptors:	Fminer backbone refinement
Training dataset:	Excel sheet , RDF/XML (expe
Feature dataset:	RDF/XML , YAML (experts, d
Model:	RDF/XML , YAML (experts, m
Validation:	
Detailed report:	show
Number of predictions	76
Correct predictions:	76.00 %
Weighted area under ROC:	0.904
Specificity:	0.771
Sensitivity:	0.756
Confusion Matrix:	

		Mea
		active
Predicted	active	31
	inactive	10

Crossvalidation report

Created at 03.02.2011 - 03:01

Table of Contents

Mean Results

This section contains results.

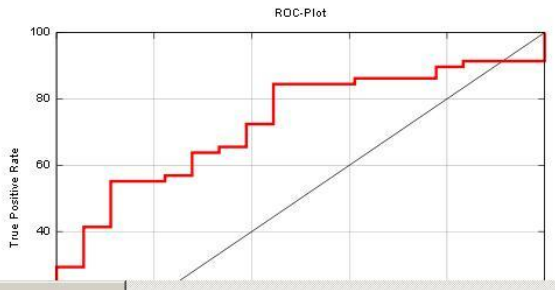
Table 1. Mean Results

Algorithm uri	http://webservices.in-silico.ch/algorithm/lazar
Dataset uri	http://webservices.in-silico.ch/dataset/1702
Num folds	10
Percent correct	69.17 +- 475.31
Weighted area under roc	0.90
Area under roc	true: 0.94, false: 0.89 +- true: 0.03, false: 0.05
F measure	true: 0.78, false: 0.73
True positive rate	0.77
True negative rate	0.77

Roc Plot

This section contains the roc plot.

Figure 1. Roc plot



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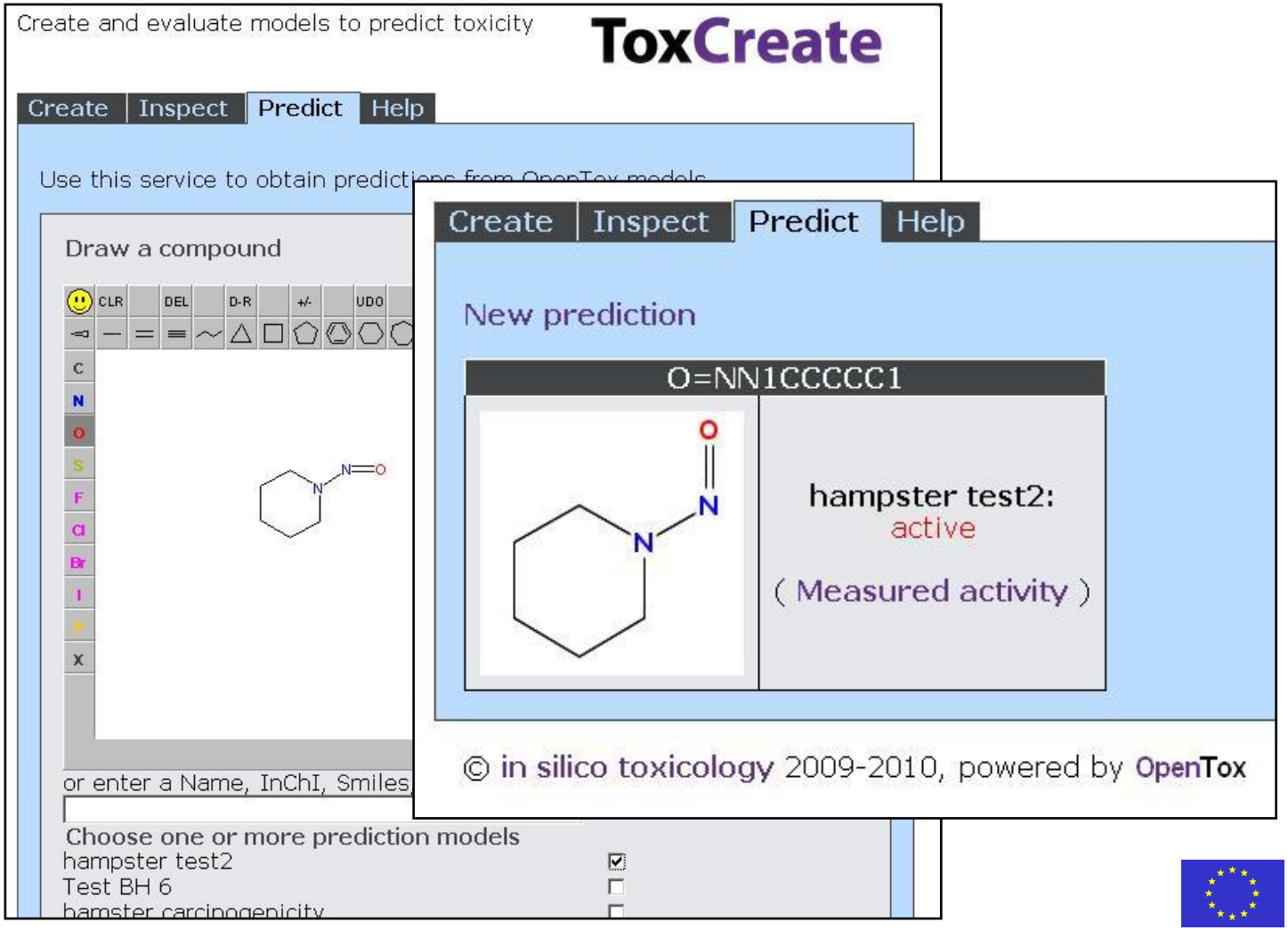
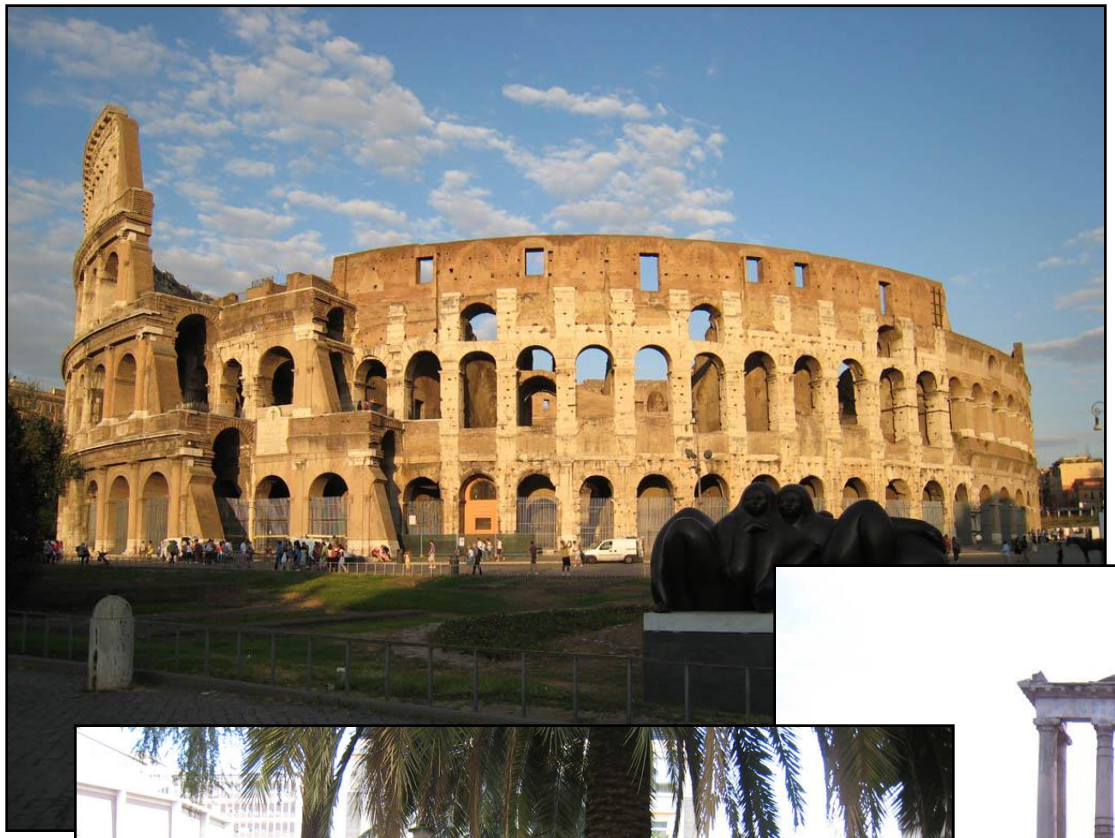
ToxCreate (3)

Step 3: enter new structure to predict…

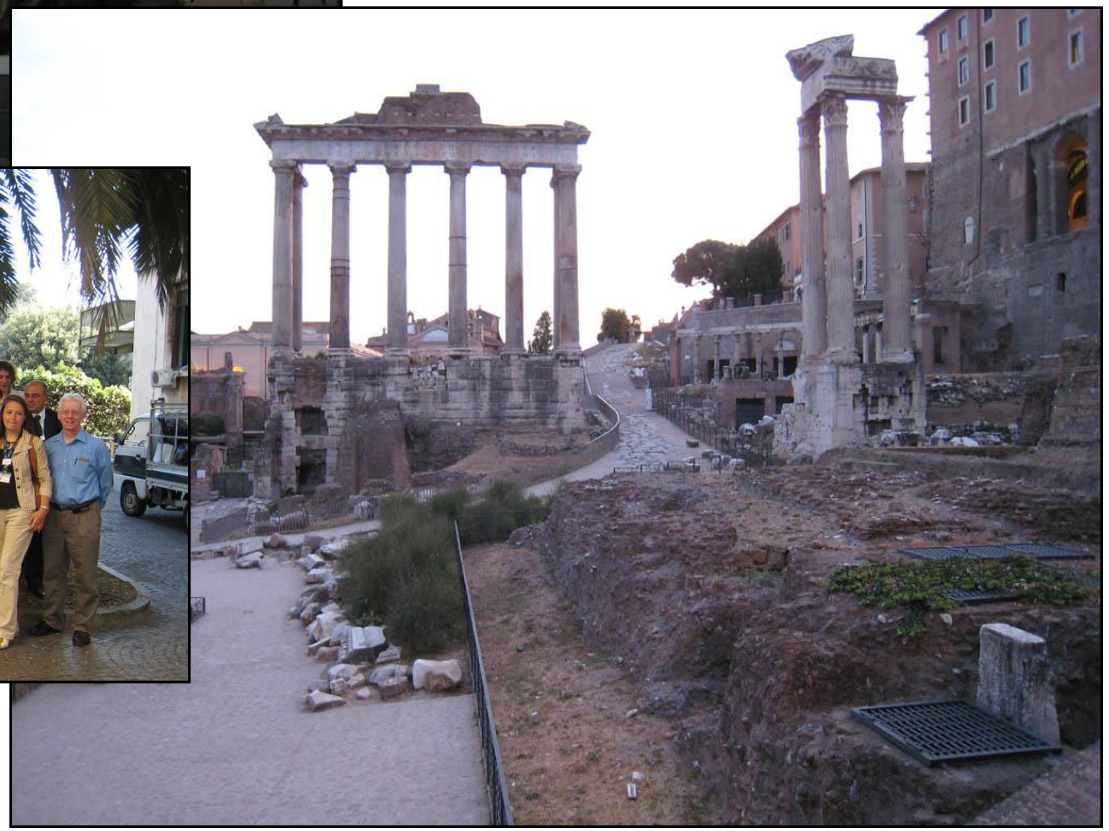




Rome, Italy

Sept. 2009

OpenTox 2nd meeting



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OpenTox Implementation Outline

- **User Needs**
- **Semantic Web for Predictive Toxicology**
- **Key Components**
- **Web Service Interoperability**
  - Bioclipse, CDK
  - Synergy Pilots

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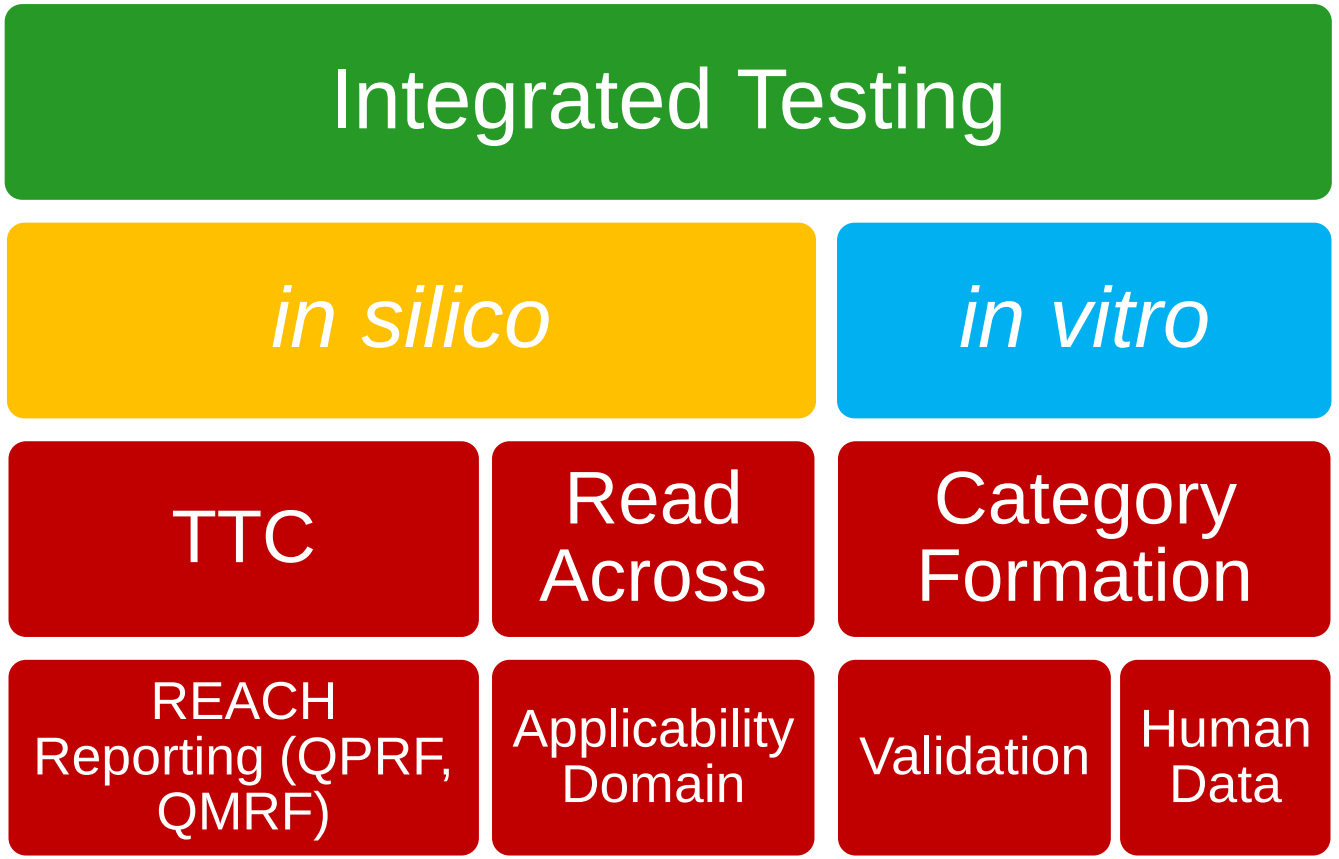
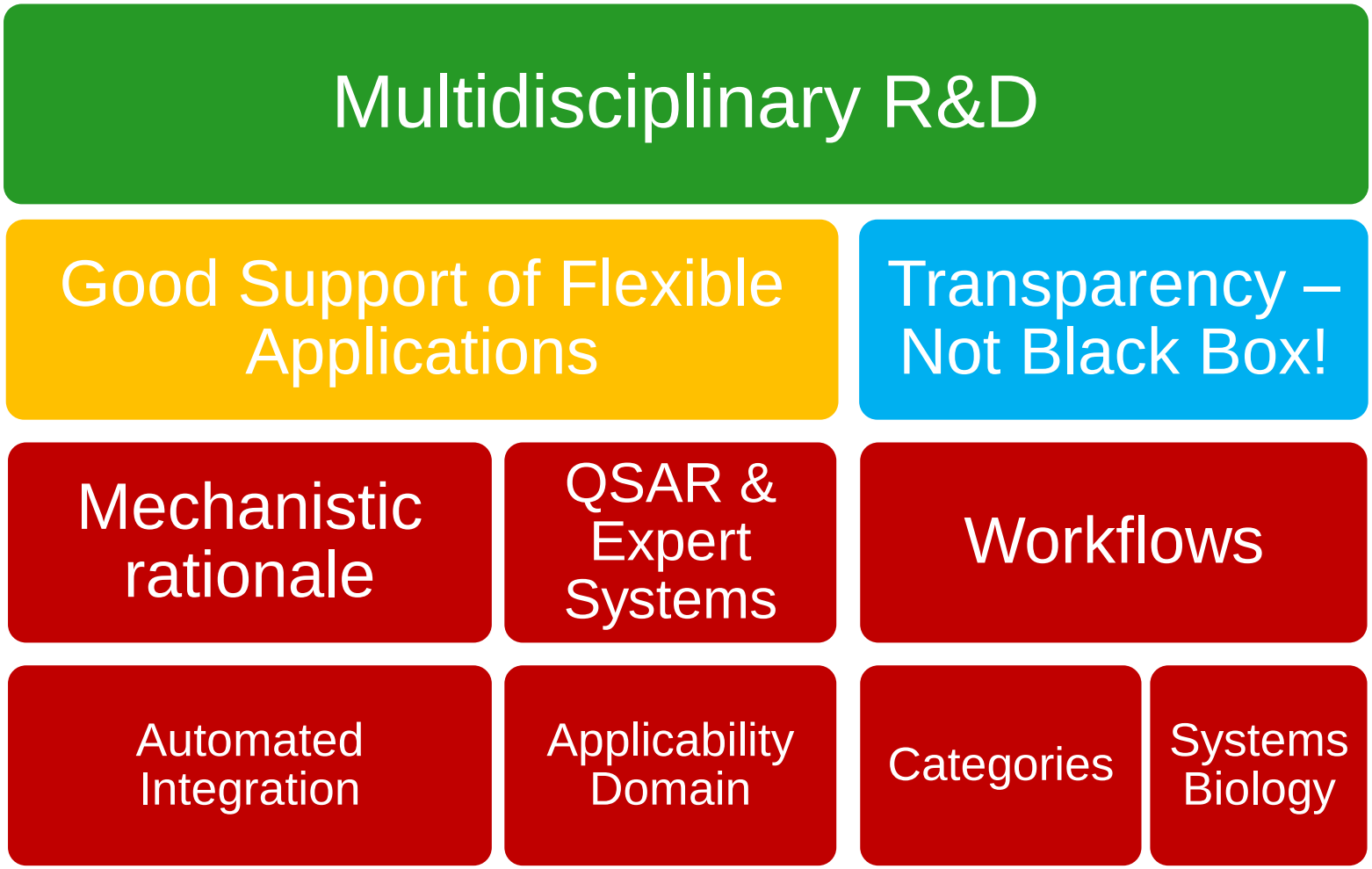
Compelling User Needs, 1



Communicated to OpenTox in 2009 by Grace Patlewicz (Du Pont)

TTC: Threshold of Tox Concern. QPRF: QSAR Prediction Reporting Format.
QMRF: QSAR Model Reporting Format.

Compelling Users Needs, 2



Communicated to OpenTox in 2009 by Stephanie Ringeissen (L'Oréal)

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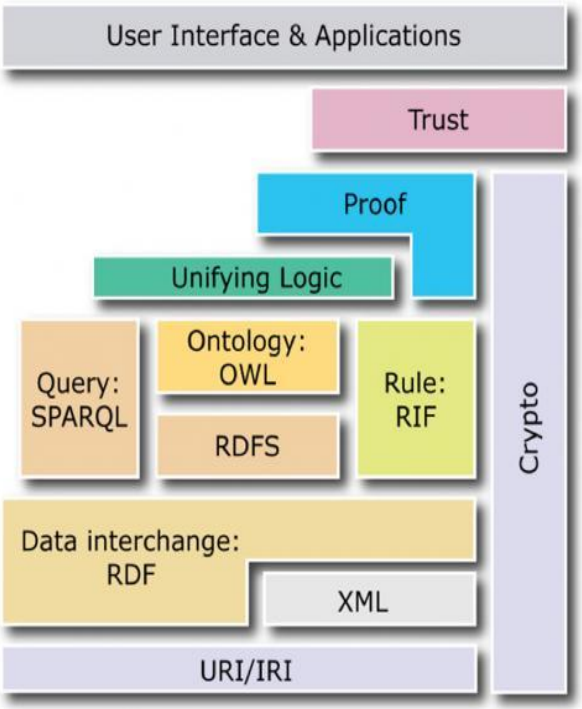
Semantic Web for Predictive Toxicology

- **URIs**: Uniform Resource Identifier on the web with a name & location
- **RDF:** Resource Description Framework - Graph based Data interchange model to structure data and link resources
- **OWL**: Ontology (Web) Language to add vocabulary for describing properties and relationships



A www network of Linked Resources for Predictive Toxicology!

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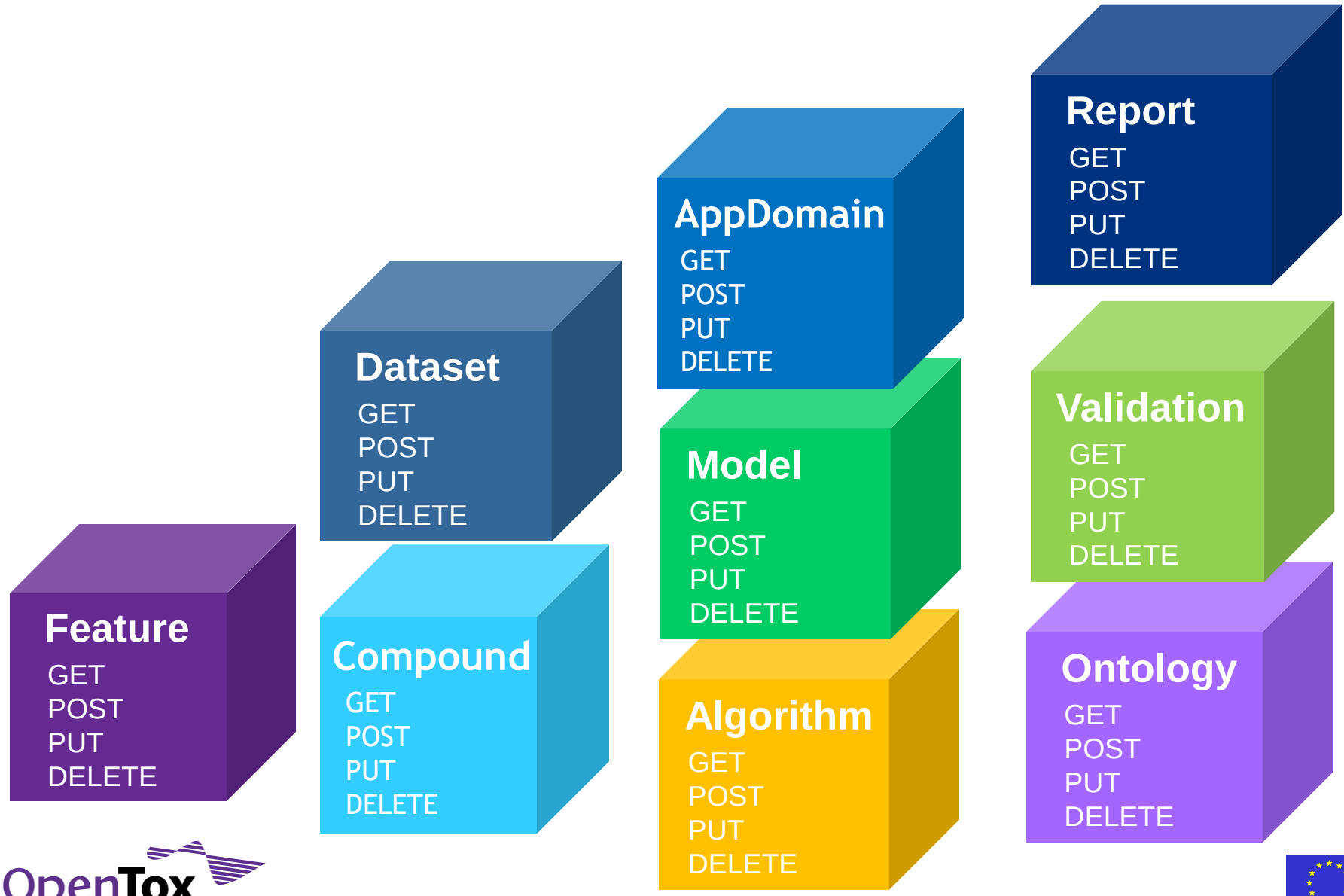
OpenTox Web Linked Resources



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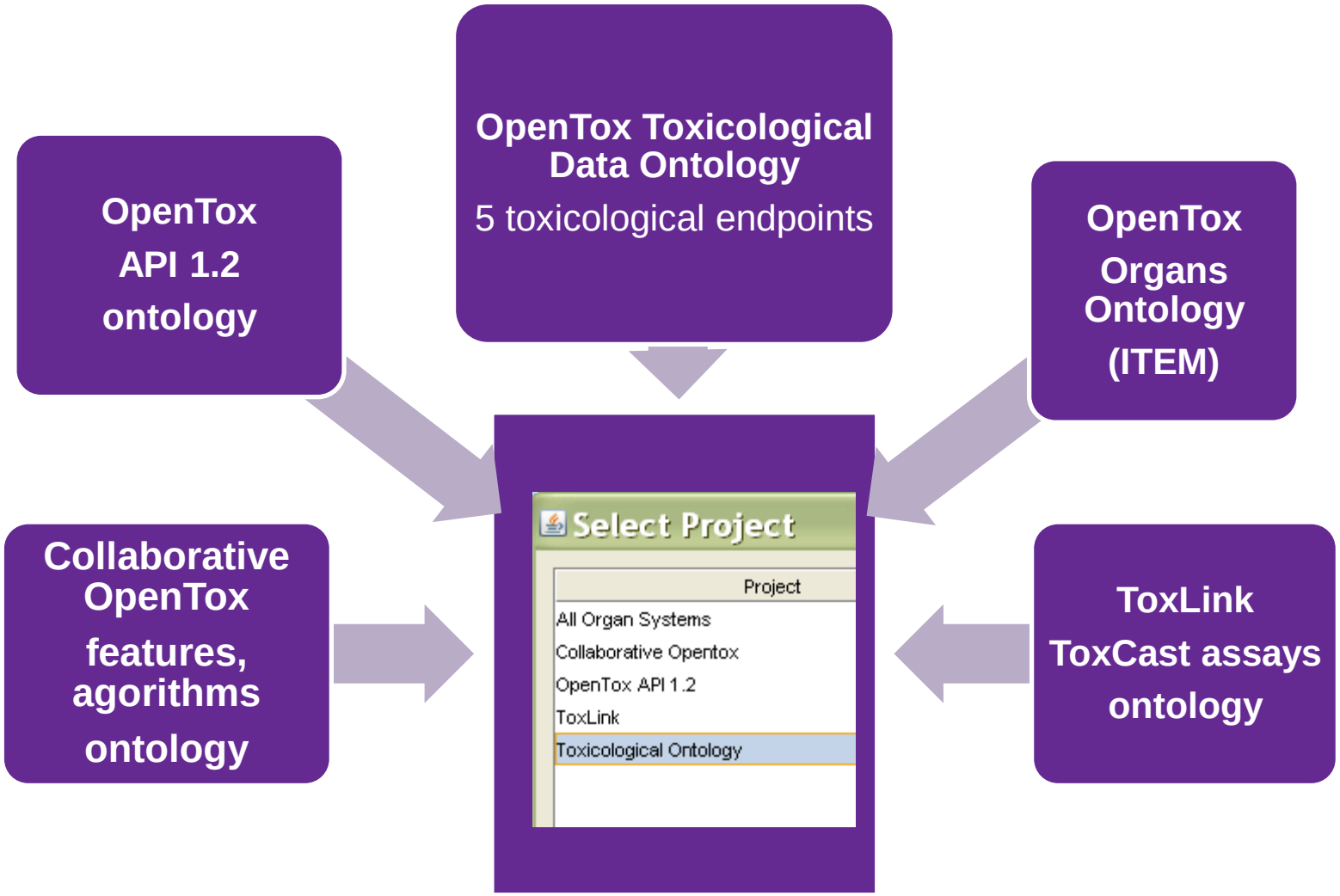
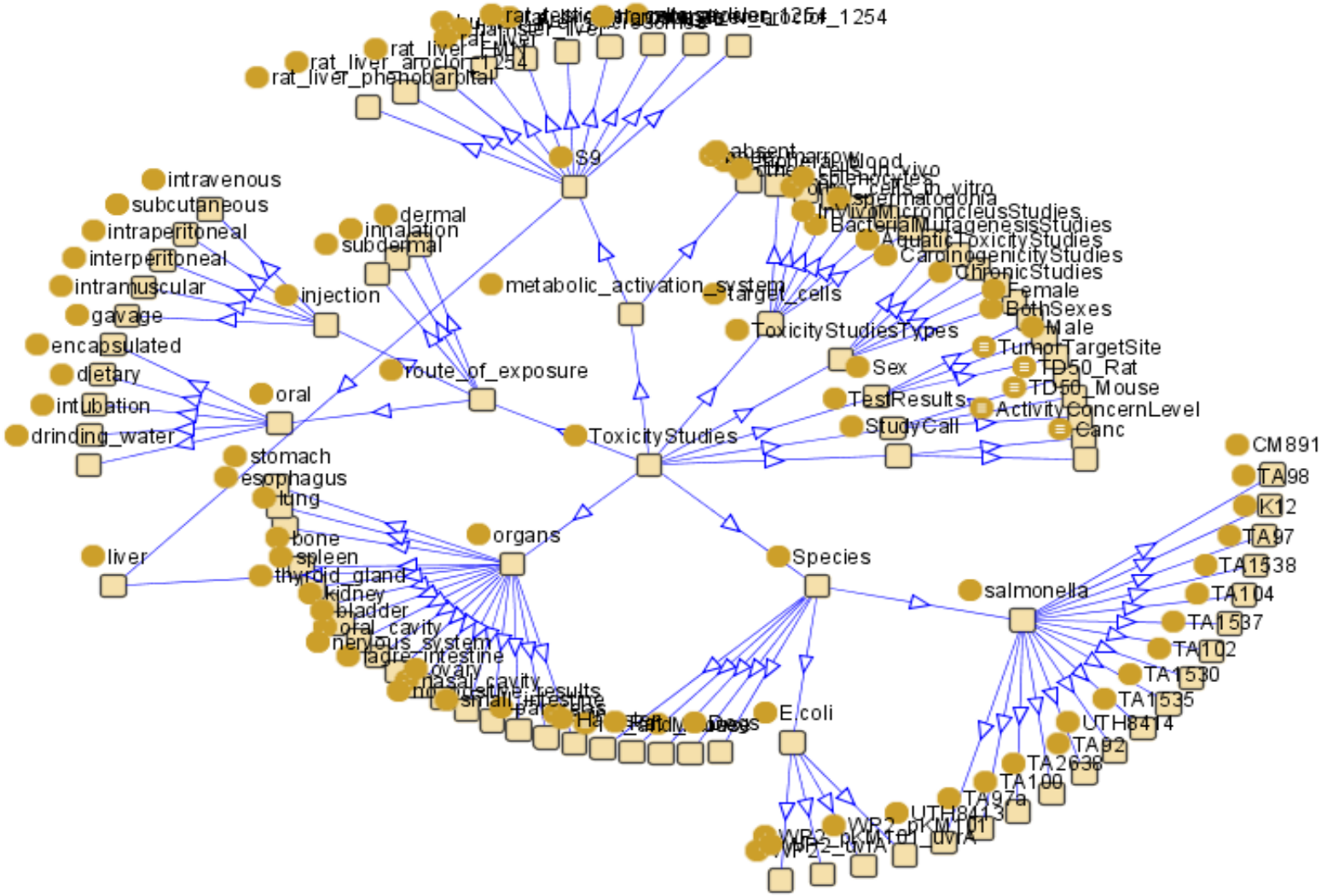
Collaborative Ontology Development: Collaborative Protege Server



www.opentox.org/dev/ontology/collaborative_protege

Toxicological Ontology: Graphical Representation



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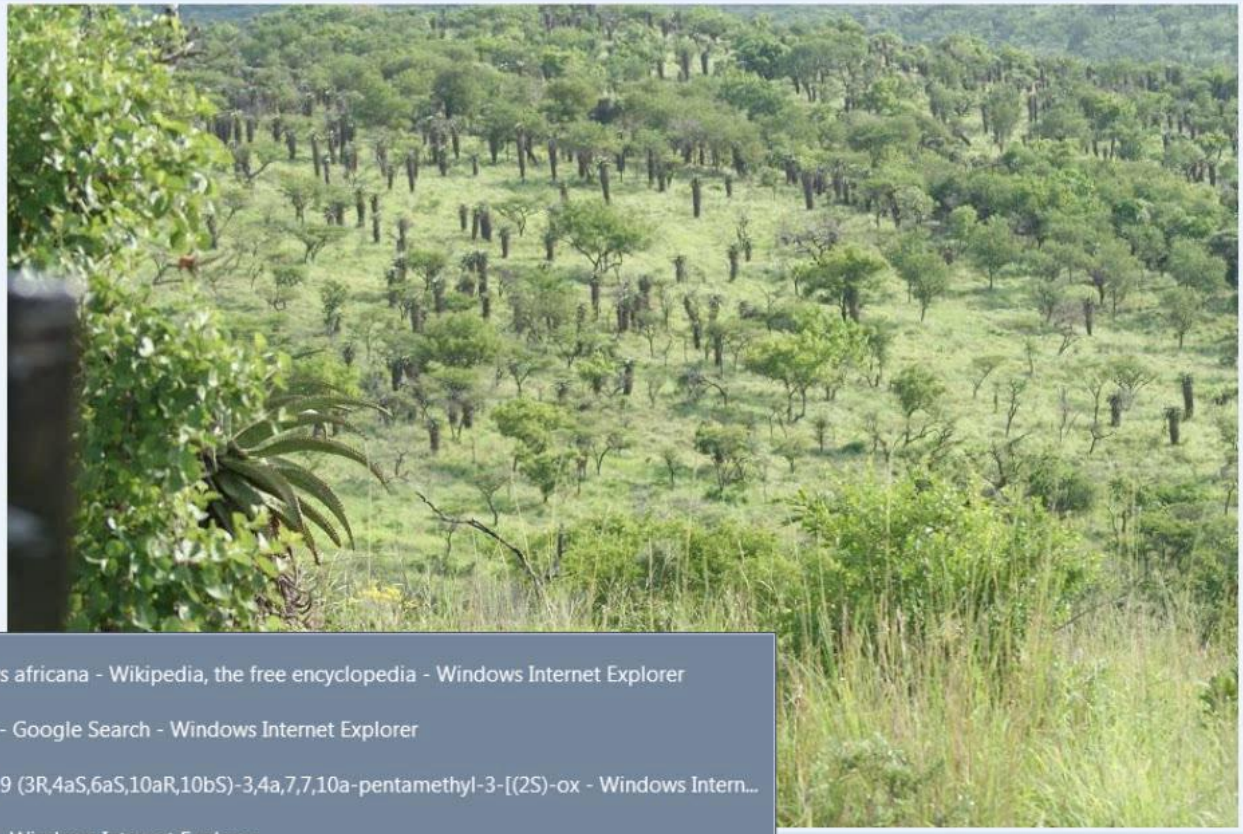
Web service interoperability

Bioclipse, CDK, Synergy

“Tamboti Tree Use Case” & Bioclipse-OpenTox Demo follows

13 Thanda Bush 101211 1.JPG - Windows Photo Viewer

File Print E-mail Burn Open



Spirostachys africana - Wikipedia, the free encyclopedia - Windows Internet Explorer

excoecarin - Google Search - Windows Internet Explorer

183900-28-9 (3R,4aS,6aS,10aR,10bS)-3,4a,7,7,10a-pentamethyl-3-[(2S)-ox - Windows Intern...

Download - Windows Internet Explorer

GoToMeeting : My Meetings - Windows Internet Explorer

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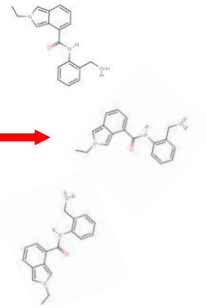
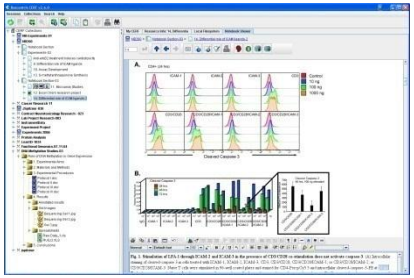
Synergy Drug Design Collaboration Pilot

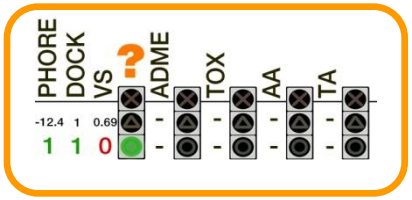


Screened Library

Data



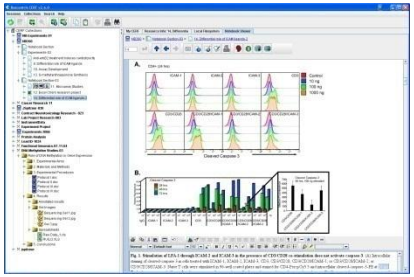
CERF



Refine Predictions

SYNERGY

Data



Toxicity Predictions

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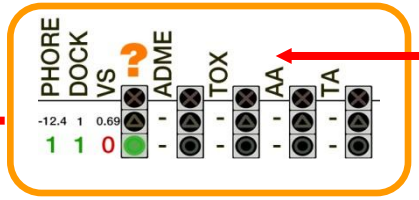
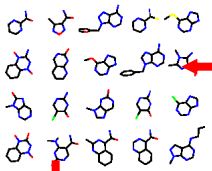
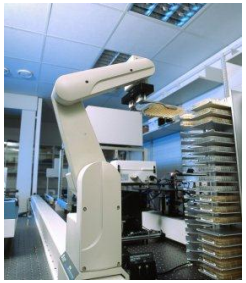
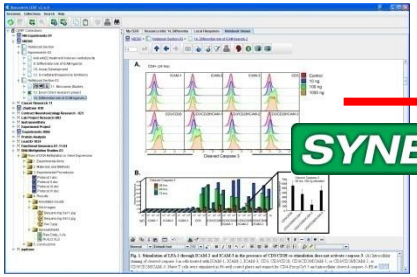


SYNERGY

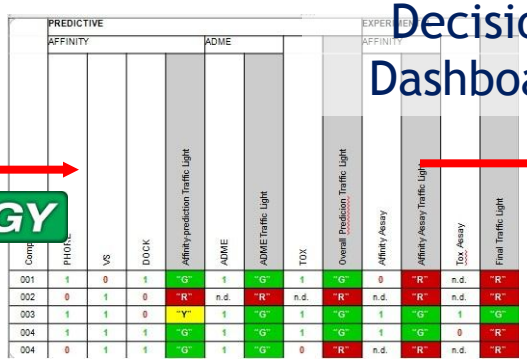




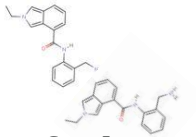
Toxicity Assays



SYNERGY



Decision Dashboard



(Safer) Drug Leads

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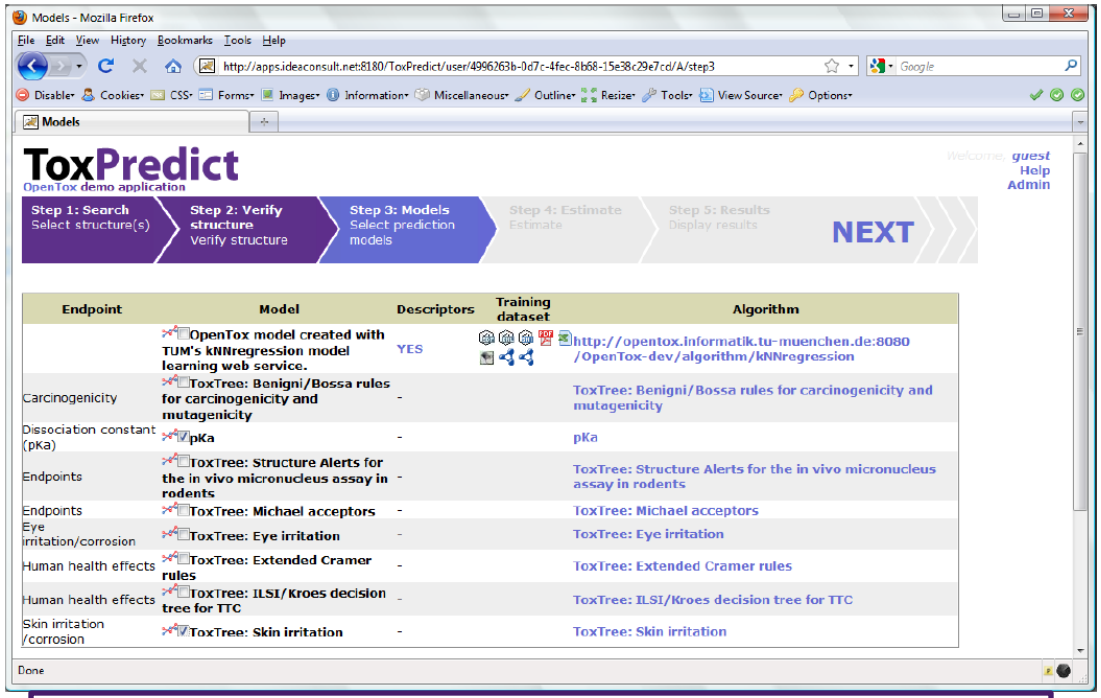
www.scientistsagainstmalaria.net

Recap: What you can do with it ...



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

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Recap: What you can do with it ...

Simple building

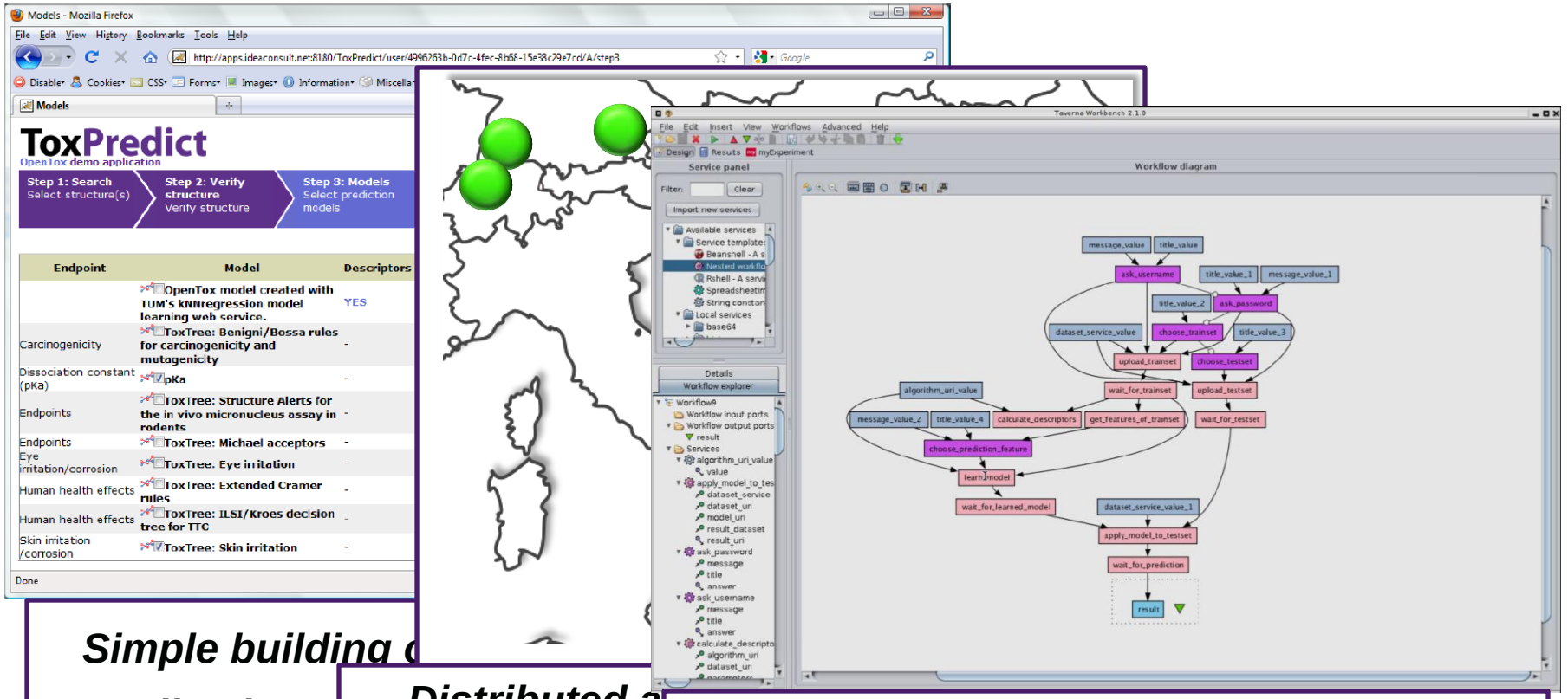
applications

methods and

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

OpenTox

Recap: What you can do with it ...



Simple building

applications

methods and

Distributed a

wide range o

methods

Integration into workflow systems for computational chemistry & biology

OpenTox

Journal of Cheminformatics Publication

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 Jeliazkova, Vedrin Jeliazkov, Ivelina Nikolova, Romualdo Benigni, OlgaTcheremenskaia, Stefan Kramer, Tobias Girschick, Fabian Buchwald, JoergWicker, 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 Gloriozova, Sergey Novikov, Natalia Skvortsova, Dmitry Druzhilovsky, Sunil Chawla, Indira Ghosh, Surajit Ray, Hitesh Patel and Sylvia Escher

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

OpenTox

OpenTox Achievements to Date:

- ✓ **Integrated services:** prediction models & creation, descriptors, validation
- ✓ **Integrated databases:** ToxCast, ISS, Fraunhofer Inst., Leadscope
- ✓ **Ontologies**: Organs, Toxicological end-points
- ✓ **OpenToxipedia:** terminology related to the study of toxicity
- ✓ **Prototype applications published:** ToxPredict, ToxCreate
- ✓ **API & framework design:** freely available from open source repository
- ✓ **Integration and interoperability:** e.g. OpenTox with Bioclipse & CDK

OpenTox

API: Application Programming Interface, ISS: Superior Health Institute, Italy
Bioclipse: free, open source workbench for the life sciences.
CDK: open source Java library for Chemoinformatics and Bioinformatics.

Rhodos, Greece

Sept. 2010

OpenTox 3rd meeting

EuroQSAR 2010

OpenTox

Acknowledgements

FUNDING: European Union, Seventh Framework Program: HEALTH-2007-1.3-3 Promotion, development, validation, acceptance and implementation of QSARs (Quantitative Structure-Activity Relationships) for toxicology, Project Reference Number Health-F5-2008-200787 (2008-2011).

Douglas Connect, Switzerland (P.I.)

In Silico Toxicology, Switzerland

Ideaconsult, Bulgaria

David Gallagher, UK

Seascape Learning & JNU, India

Superior Health Institute (ISS), Italy

Technical University of Munich, Germany

Albert Ludwigs University Freiburg, Germany

Fraunhofer Institute for Toxicology & Experimental Medicine, Germany

Institute of Biomedical Chem. of the Russian Acad. of Medical Sci., Russia

National Technical University of Athens, Greece

OpenTox

Invitation to OpenTox in Munich, Aug. 2011

OpenTox InterAction Meeting
Innovation in Predictive Toxicology

Modelling, Applications, REACH, Risk Assessment

9-12 August 2011
Technical University of Munich, Germany

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

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

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

More Information at:
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