Development and Use of Predictive Toxicology Applications

OpenTox Presentation

19 October 2010

University Uppsala, Sweden

Barry Hardy (Douglas Connect)

OpenTox

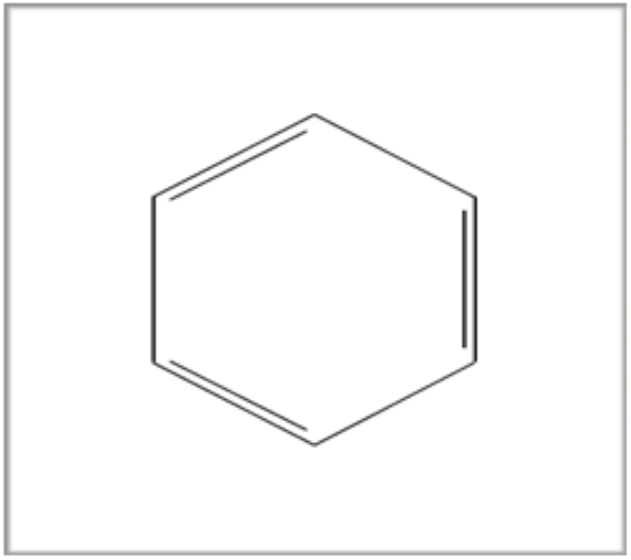
SEVENTH FRAMEWORK PROGRAMME

ToxPredict

OpenTox demo application

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

Download as



CAS RN	71-43-2
EINECS	200-753-7
IUPAC name	benzene
Synonym	(6)annulene; benzine; Benzol; Benzolene; bicarburet of hydrogen; carbon oil; Coal naphtha; cyclohexatriene; mineral naphtha; motor benzol; nitration benzene; Phene; Phenyl hydride; pyrobenzol.
Synonym	21742.0
Synonym	Benzene
Synonym	benzene
Quality label	OK

MolecularWeight MolecularWeight

MW	78.1112

Semantic Reflections

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

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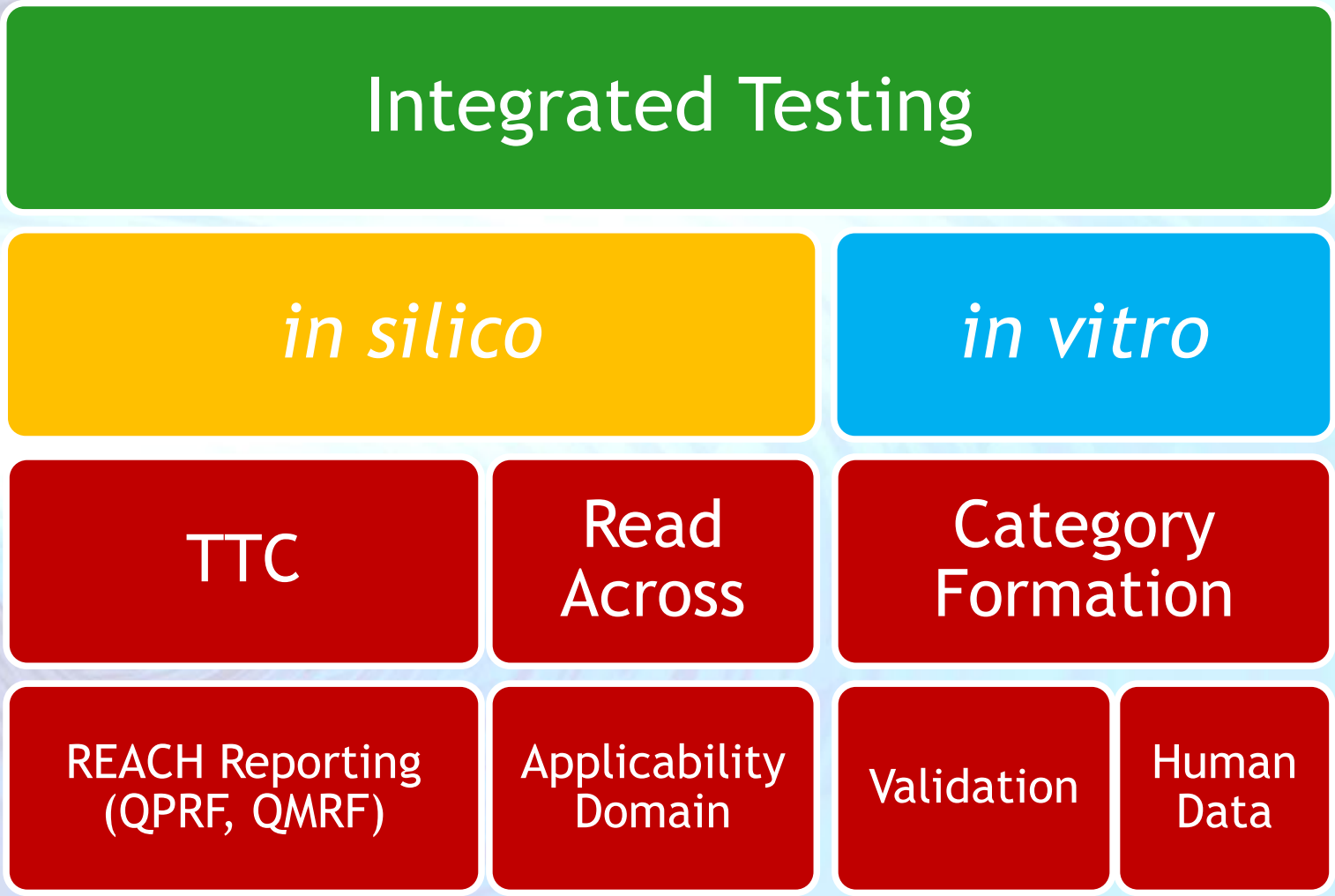
Compelling Needs of Users



Communicated in OpenTox 2009 Virtual Meeting
by Grace Patlewicz (Du Pont)

Compelling Needs of Users

Multidisciplinary R&D

Good Support of Flexible Applications

Transparency – Not Black Box!

Mechanistic rationale

QSAR & Expert Systems

Workflows

Automated Integration

Applicability Domain

Categories

Systems Biology

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Communicated in OpenTox 2009 workshop at ISS in Rome by Stephanie Ringeissen (L'Oréal)

Collaborating Partners

In Silico Toxicology, Switzerland

Douglas Connect, Switzerland

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

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

Seascape Learning & JNU, India

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OpenTox Advisory Board

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- Pharmatrope
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- U.S. Environmental Protection Agency
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- Nestlé
- Roche
- AstraZeneca
- LHASA
- Leadscope
- University of North Carolina
- EC Environment Directorate General
- Organisation for Economic Cooperation & Development
- CADASTER
- Bayer Healthcare

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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 available at
www.jcheminf.com/content/2/1/7

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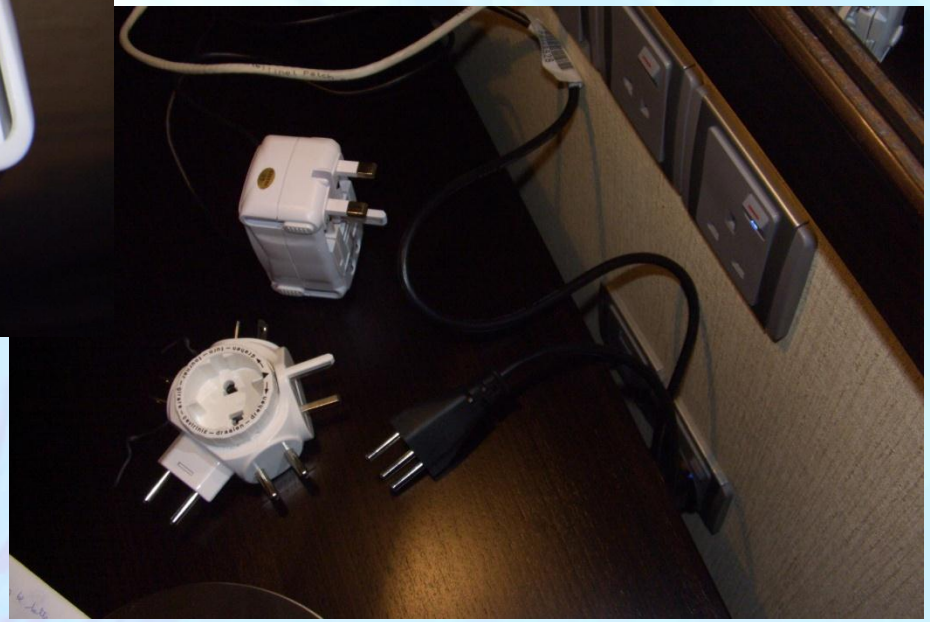
Absence of Interoperability creates Problems



Adaptor Challenge in Jeddah, 2008

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Interacting Components create Solutions

Adaptor Solution in Jeddah, 2008

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SECI Model for Knowledge Management

Tacit

Tacit

Tacit

Knowledge Sharing: Discussions

Socialisation

Externalisation

Explicit

Knowledge Creation from R&D: Data, Codes

Acceptance

Learning: Apply Models

Internalisation

Combination

Knowledege Combination: Predictive Models

Tacit

Explicit

Explicit

Explicit

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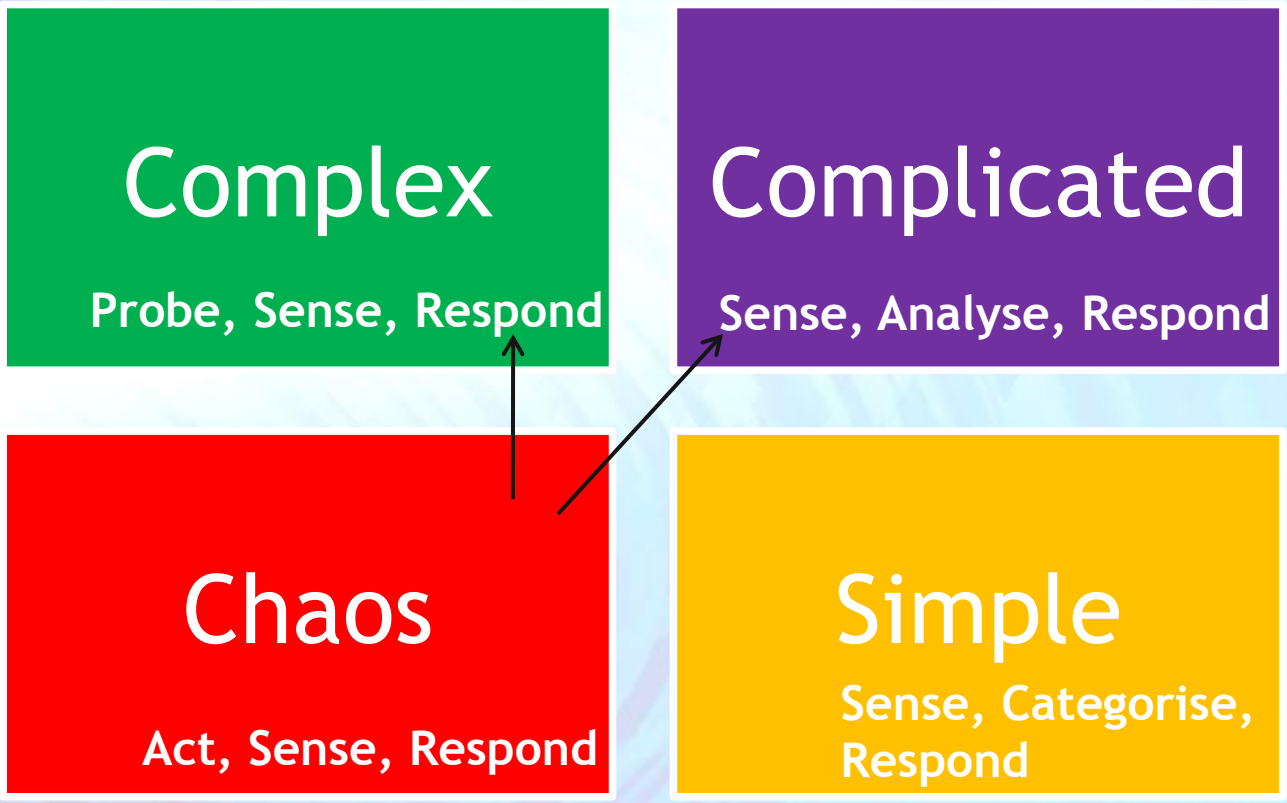
Based on Nonaka & Takeuchi, The Knowledge Creating Company, 1995

Complexity Context

Non Repeatable
Adaptative, Patterns,
Filters

Complex Cause & Effect
Systems Thinking, Analysis

Sense
Making for
Emergent
Practice



Processes
Good
Practice

Leadership
Novel
Practice

Procedures
Best
Practice

Lack of Cause & Effect, Stability-focused
Intervention, Crisis Management

Cause & Effect
Repeatable, SOPs

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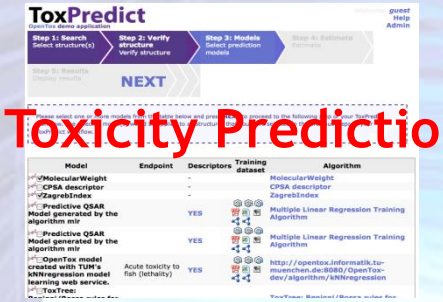
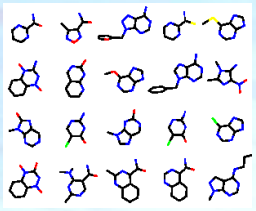
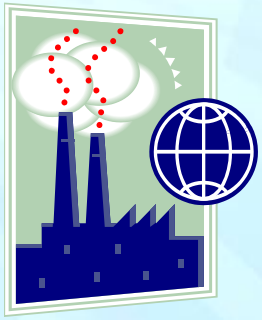
Based on the Cynefin Framework,
Dave Snowden

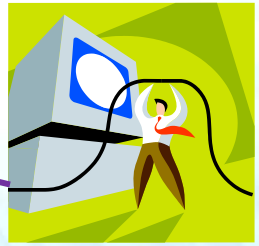
Accelerating Knowledge Flows in Predictive Toxicology

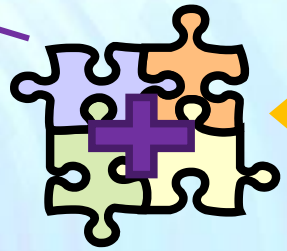


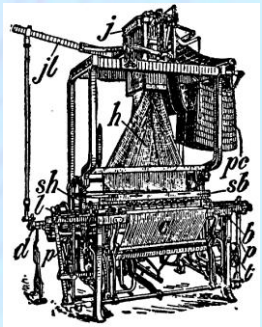
Toxicity Predictions











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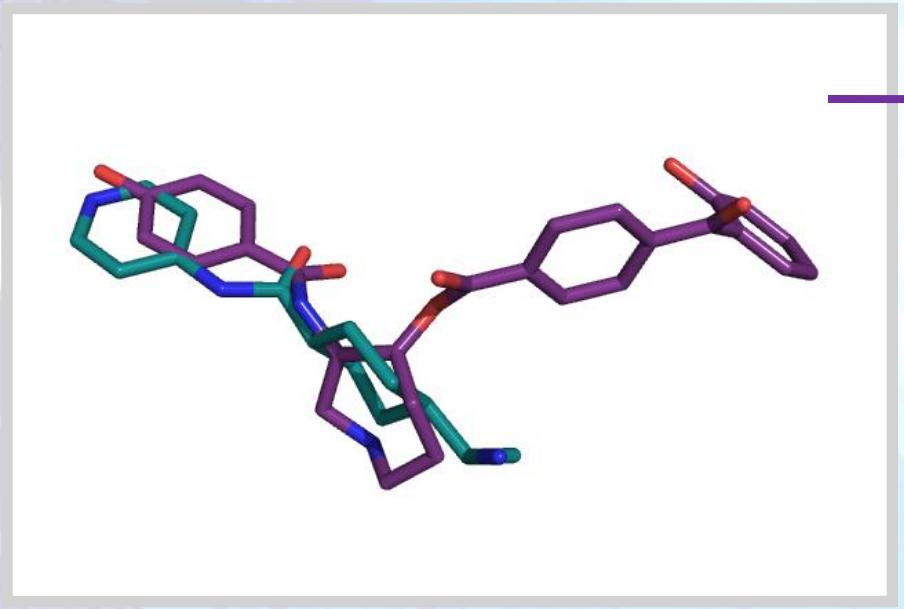
Collaborative Predictive Toxicology Challenge

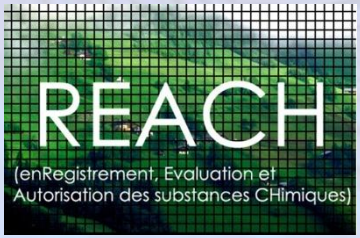
Input Structure



VO

Out – Toxic or Not?

- LD50
- Liver Toxicity
- Secondary Metabolites
- Bioavailability
- Mutagenicity
- Carcogenicity
- ReproductiveToxicology
- Skin Irritation
- Aqua Toxicity
- Combined predictions for arrays of mutiple end points



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

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REACH

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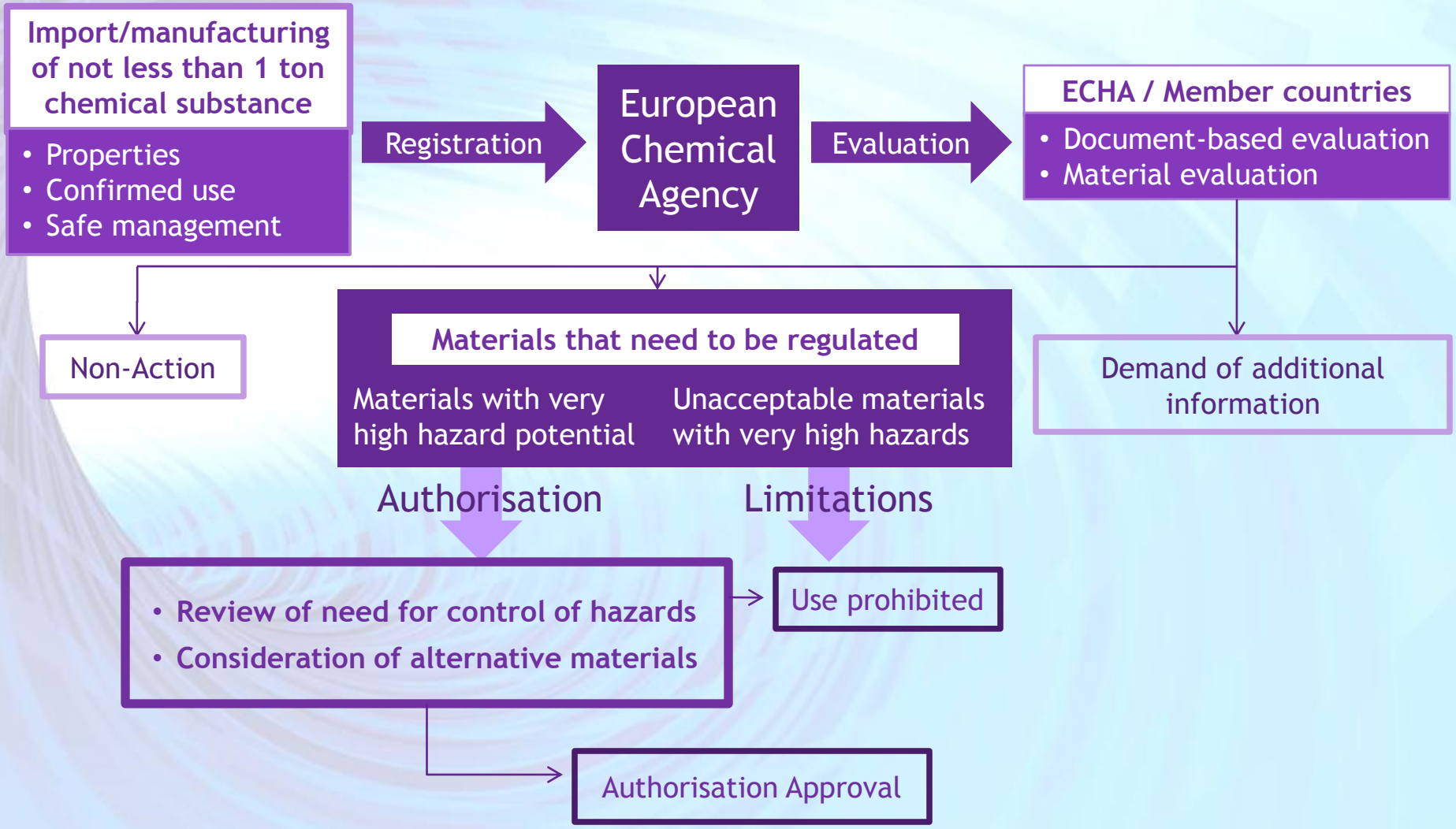
REACH Registration



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Challenges to Integrated Resources & Applications

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

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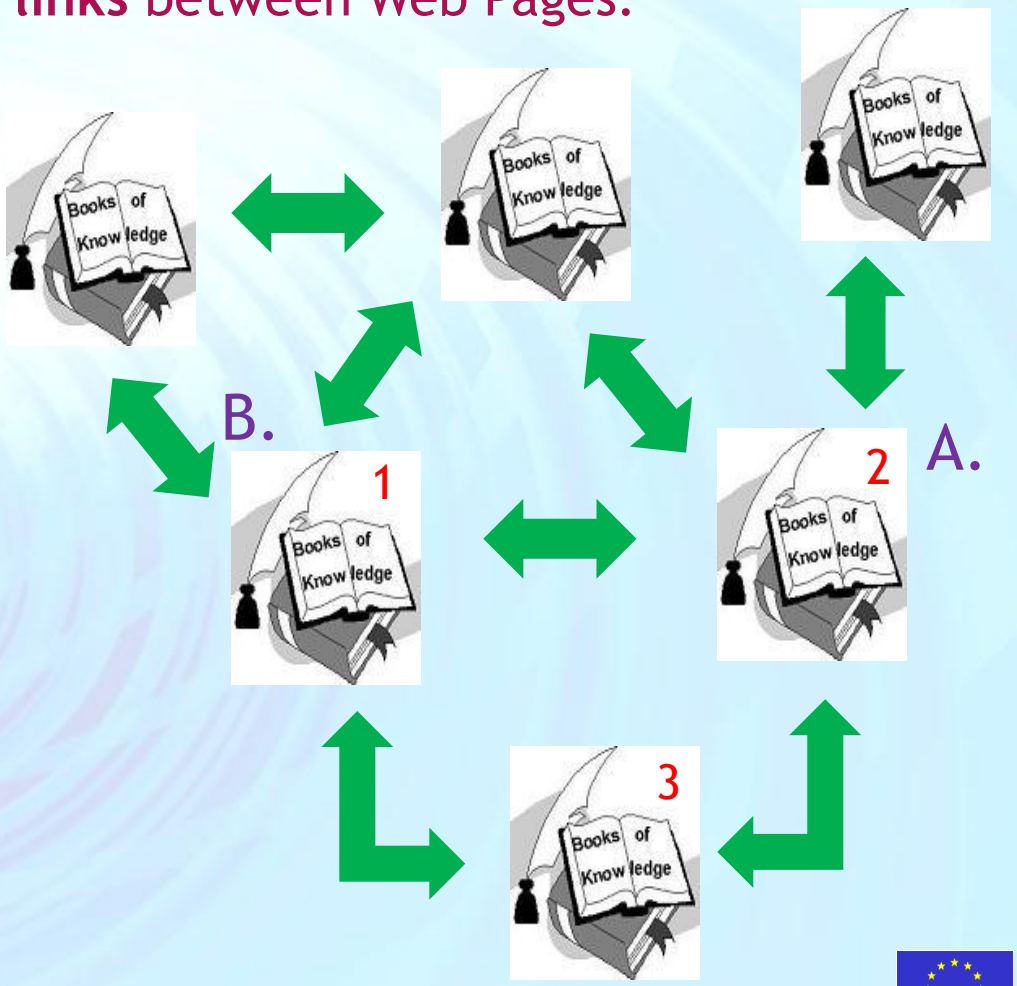
Value is in Linking

The key idea of Google's founders in creating their search engine:
There is useful knowledge in the **links** between Web Pages.

Page Ranking
A page is ranked higher in a search if:

A. it has more connections to it than other pages

B. the pages connecting to it have higher ranking themselves



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Linked Data enables Knowledge Creation, Combination and Analysis

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…

DBpedia = Linked Data approach applied to Wikipedia

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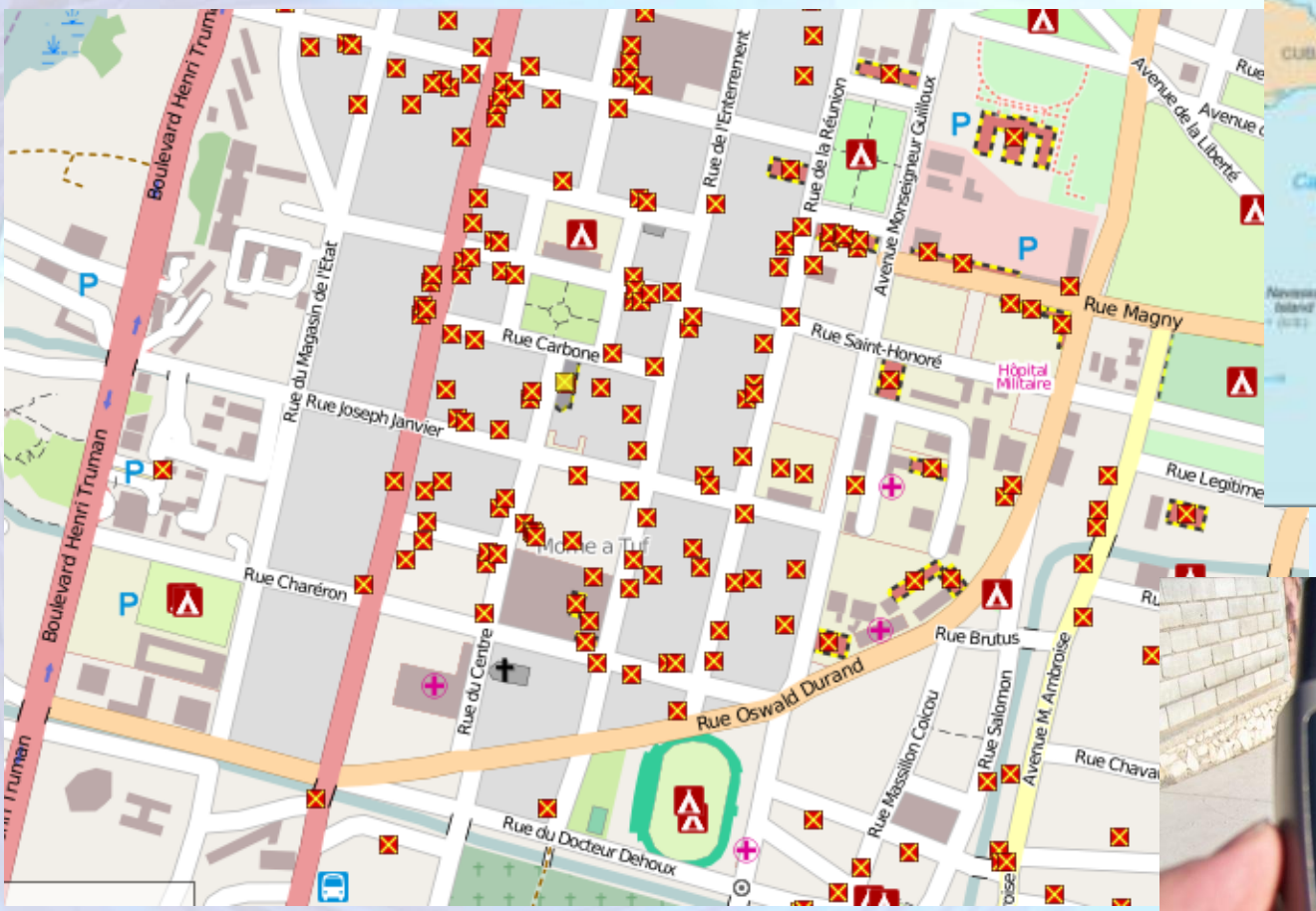
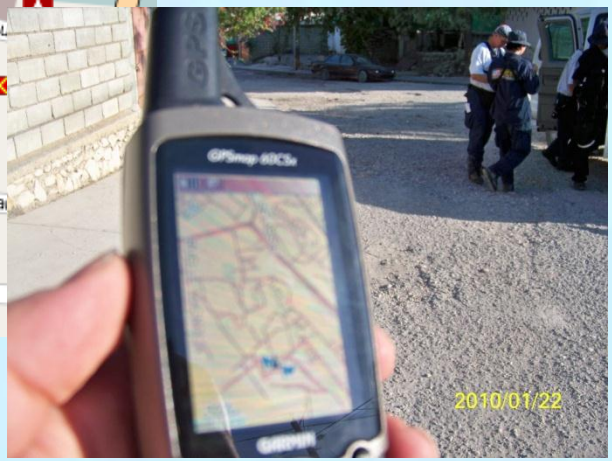
Solution created by Linked Open Data, Web Applications and Crowdsourcing





Haiti Earthquake Crisis Response (2010)

wiki.openstreetmap.org

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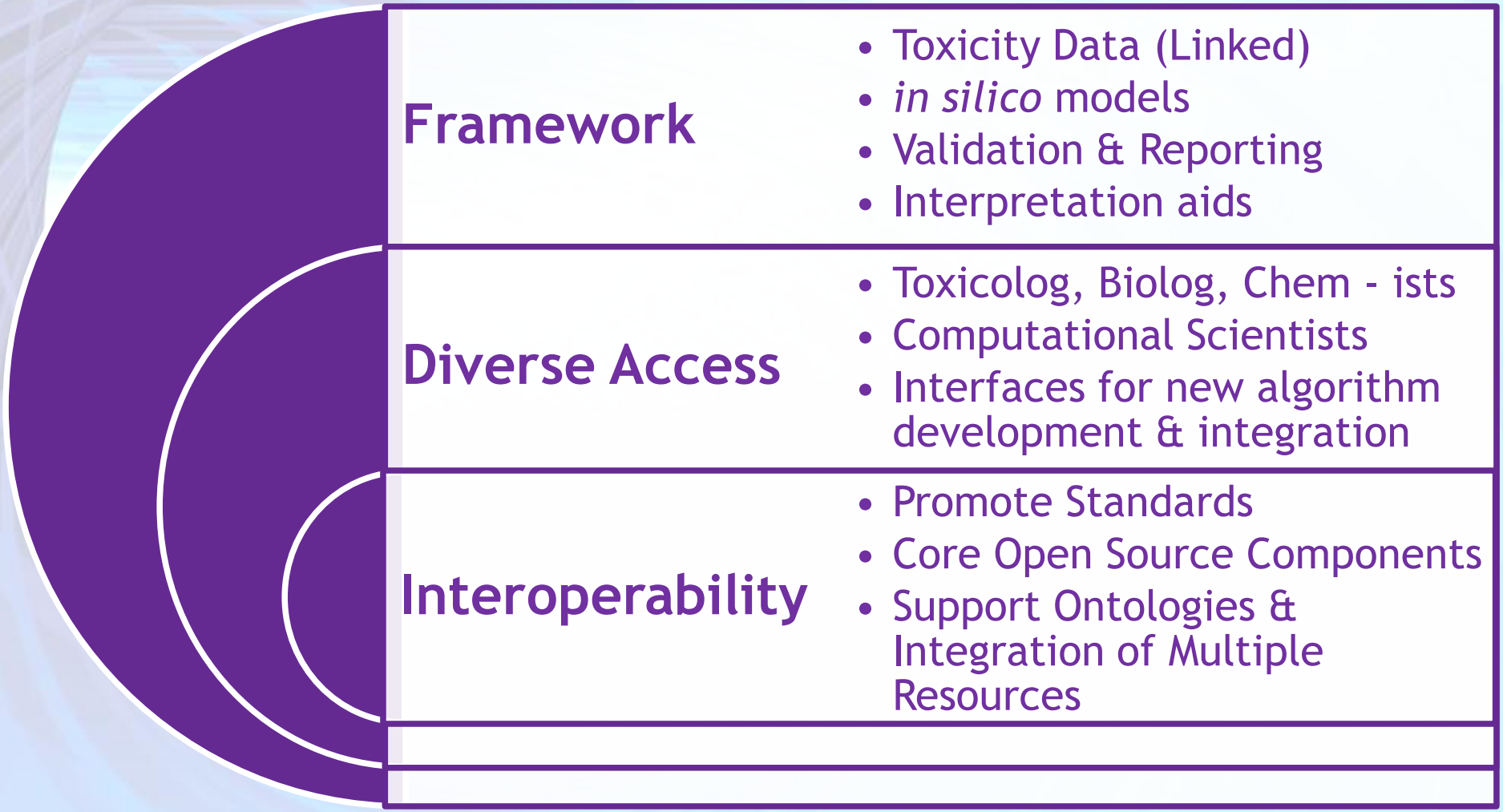
OpenTox is an Integrating Framework



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	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

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OpenTox Components

Compounds: Structures, names, ...

Features: Chemical and biological (toxicological) properties, substructures, ...

Datasets: Relationships between compounds and features

Algorithms: Instructions for solving problems

Models: Algorithms applied to data yield models which can be used for predictions

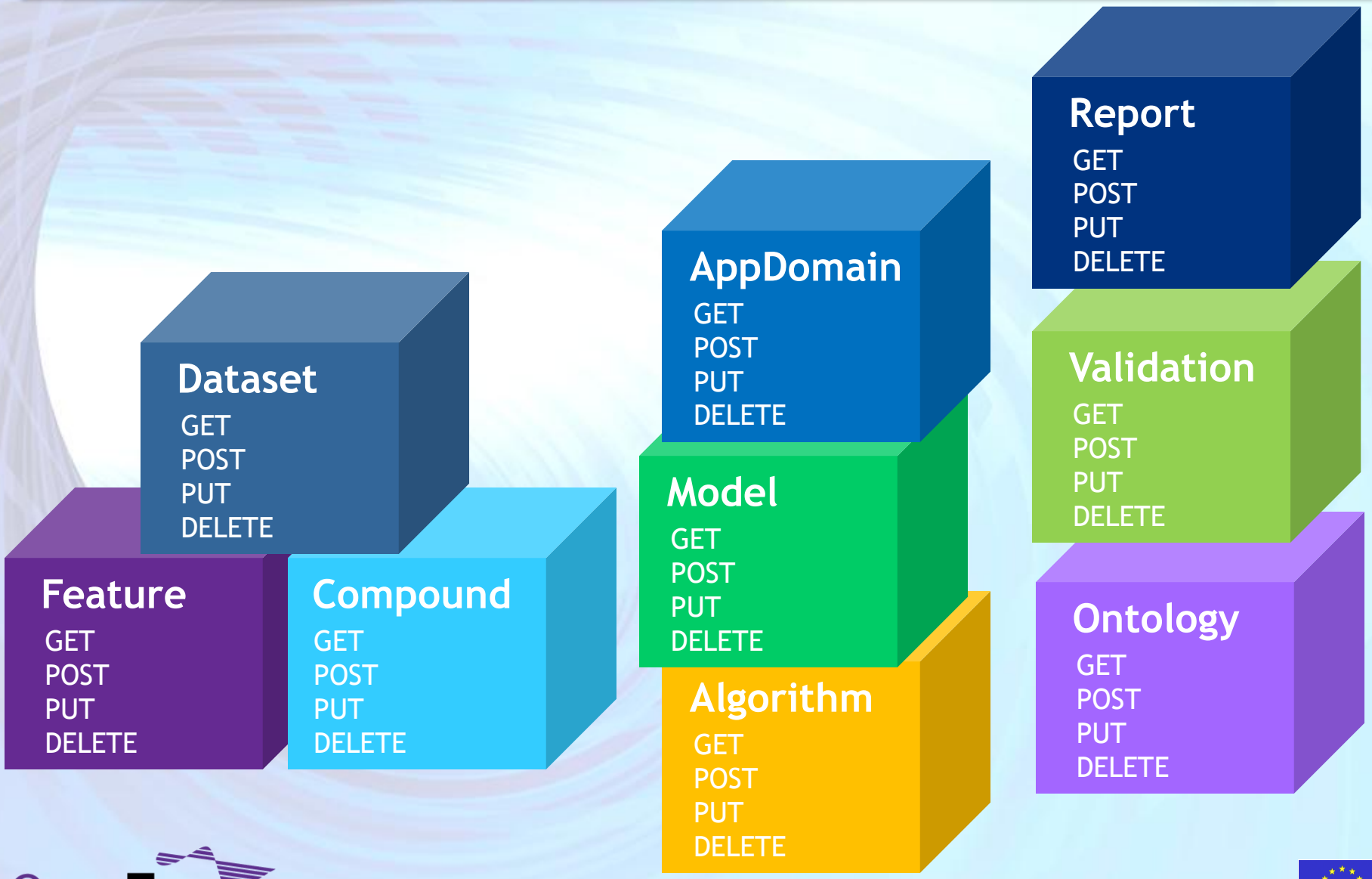
Validation: Methods for estimating the accuracy of model predictions

Reports: Report predictions and models e.g. to regulatory authorities

Tasks: Handle long running calculations

Authentification and Authorisation: Protect confidential data

Overview of Application Programming Interfaces



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Representational State Transfer (REST)

What?

- Architectural style for distributed information systems on the Web
- Simple interfaces, data transfer via **hypertext transfer protocol (HTTP)**, stateless client/server protocol
  - GET, POST, PUT, DELETE
- Each **resource** is **addressed** by its own **web address**

Why?

- **Lightweight** approach to **web services**
- **Simplifies/enables** development of **distributed and local systems**
- Language independent

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Interface Definitions

Description	Method	URI	Parameter	Result	Status codes
Get available feature URIs for a compound	GET	/compound/{cid}/feature	?**feature_uris[]**="URIto features" (optional)	Returns representation of the features as uri-list or RDF All available features are returned, if no parameter is specified.	200,404,503
Create a new feature value	POST	/compound/{cid}/feature	?**feature_uri**="URIto feature" (mandatory, single feature)&**value**=the_value	URI of the compound with the new feature, e.g. /compound/{id}?feature_uris[]=the-new-feature	200,400,503
Update a new feature value	PUT	/compound/{cid}/feature	?**feature_uri**="URIto feature" (mandatory, single feature)&**value**=the_value		200,400,404,503
Delete specified features from the compound	DELETE	/compound/{cid}/feature	?**feature_uris[]**="URIto features" (optional)		200,400,404,503

Interface Definitions

Description	Method	URI	Parameters	Result	Status codes
get description of a specific feature definition	GET	/feature/{id}	-	URI-list or RDF representation of a feature.	200,404,503
create a new feature	POST	/feature	**Content-type**="any-of-RDF-types", content=RDF-representation	URI of the new feature definition.	200,400,404,503
update feature	PUT	/feature/{id}	**Content-type**="any-of-RDF-types", content=RDF-representation	-	200,400,404,503
delete feature	DELETE	/feature/{id}	-	-	200,400,404,503
get a list of available feature definitions	GET	/feature	?**query**=URI-of-the-owl:sameAs-entry	URI list or RDF of features found by the query or all available, if query is empty. Returns all features, for which owl:sameAs is given by the query.	200,404,503

Interface Definitions

Description	Method	URI	Parameters	Result	Status codes
Get a list of available datasets	GET	/dataset	Query parameters (optional, to be defined by service providers).	List of URIs or RDF for the metadata only.	200,404,503
Get a dataset	GET	/dataset/{id}	–	Representation of the dataset in a supported MIME type.	200,404,503
Query a dataset	GET	/dataset/{id}	**compound_uris[]** and/or **feature_uris[]** to select compounds and features; further query parameters may be defined by service providers.	Representation of the query result in a supported MIME type.	200,404,503
Get metadata for a dataset	GET	/dataset/{id}/metadata	–	Representation of the dataset metadata in a supported MIME type.	200,404,503
Get a list of all compounds in a dataset	GET	/dataset/{id}/compounds	–	List of compound URIs.	200,404,503
Get a list of all features in a dataset	GET	/dataset/{id}/features	–	RDF or List of feature URIs (pointing to feature definitions/ontologies).	200,404,503

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www.opentox.org/dev/apis

Interface Definitions

Description	Method	URI	Parameters	Result	Status codes
Get a list of all available models	GET	/model	(optional) ?query=URI-of-the-owl:sameAs-entry	List of model URIs or RDF representation. If query specified, returns all models, for which owl:sameAs is given by the query.	200,404,503
Get the representation of a model	GET	/model/{id}	-	Representation of the model in a supported MIME type.	200,404,503
Delete a model	DELETE	/model/{id}	-	-	200,404,503
Apply a model to predict a dataset	POST	/model/{id}	**dataset_uri** **result_dataset**=datasetsuri **dataset_service**=datasetserviceuri	URI of created prediction dataset (predictions are features), task URI for time consuming computations.	200,202,400,404,500,503
Apply a model to predict a compound	POST	/model/{id}	**compound_uri**	Prediction in a supported MIME type; task URI for time consuming computations.	200,202,400,404,500,503

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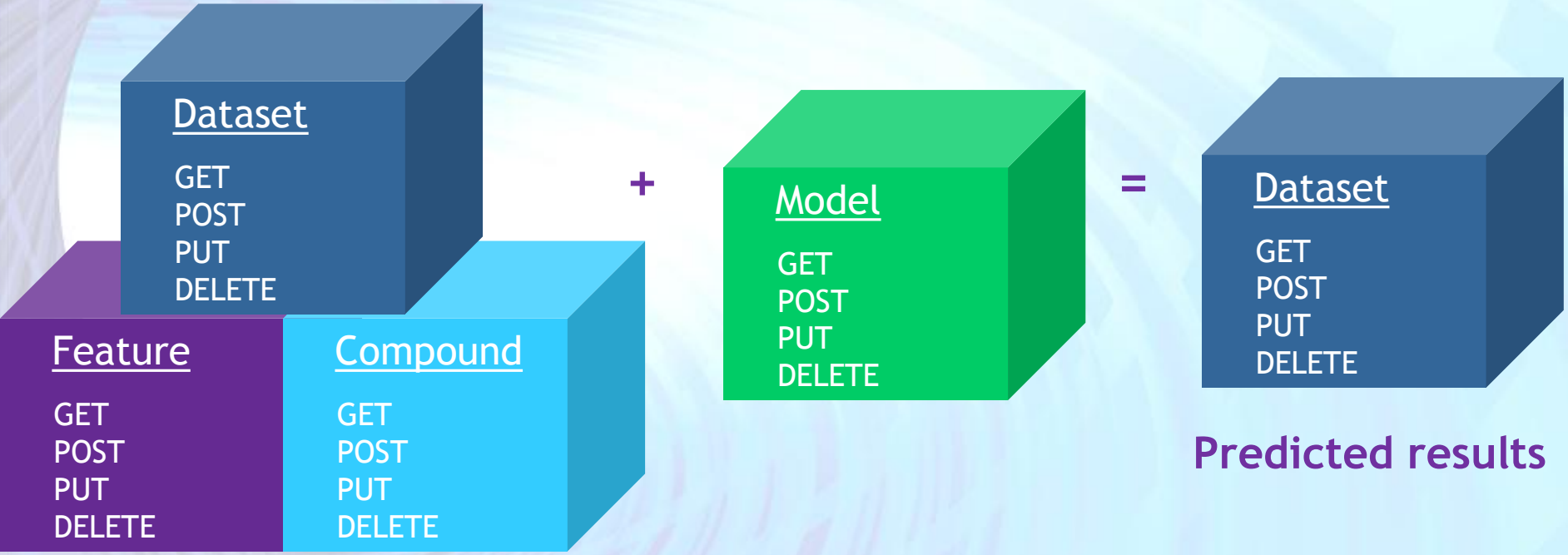
www.opentox.org/dev/apis

Interface Definitions

Description	Method	URI	Parameters	Result	Status codes
Retrieve SPARQL query results	GET	/ontology	**?query**=SPARQL_QUERY (mandatory)	RDF representation of the query results.	200,404,500
Predefined query to retrieve all models	GET	/ontology/models		RDF representation of all models.	
Predefined query to retrieve all endpoints	GET	/ontology/endpoints		RDF representation of all endpoints.	
Predefined query to retrieve all algorithms	GET	/ontology/algorithms		RDF representation of all algorithms.	
Submit SPARQL query and/or OpenTox service URL	POST	/ontology	**uri**[]=URL of a OpenTox RDF resource **query**=SPARQL_QUERY	RDF representation of the query results, if **query** is specified. if **uri[]** is specified, the server retrieves a RDF representation and adds it to the RDF storage, thus making it available for the subsequent queries.	200,404,500,502

Uniform access to calculations

Read data from a web address - process - write to a web address



Predicted results

http://myhost.com/dataset/newcompounds

http://myhost.com/model/predictivemodel1

http://myhost.com/dataset/predictedresults1

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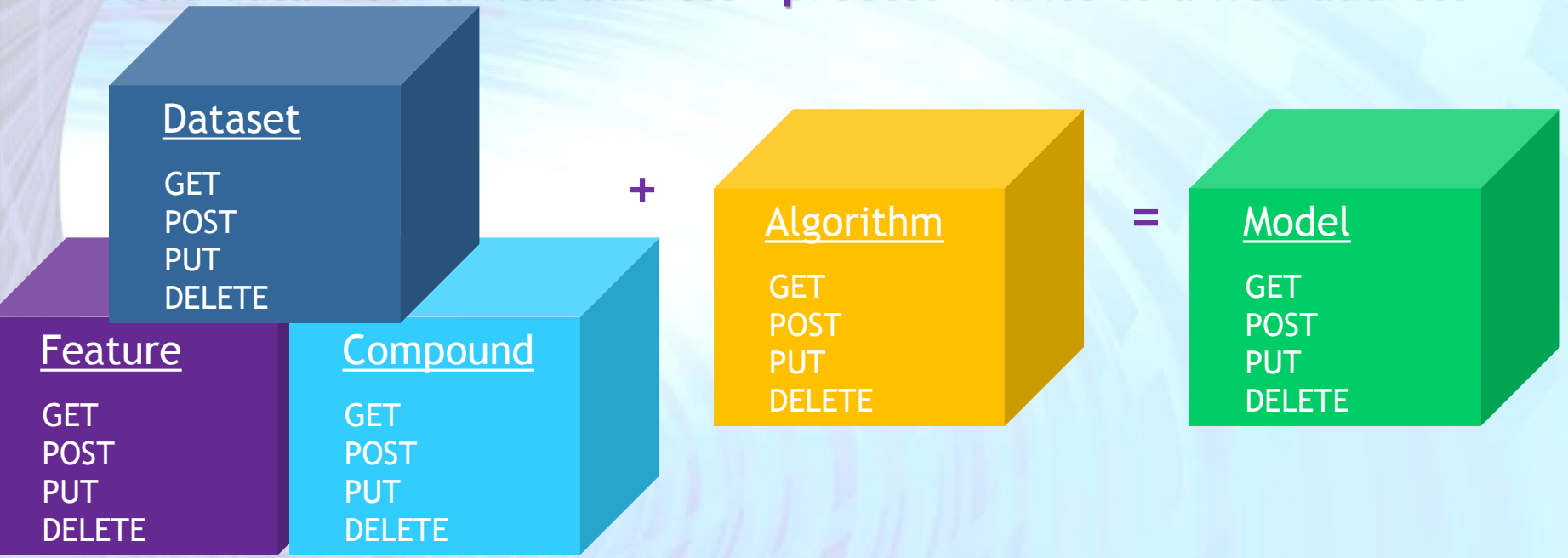
Uniform approach to models creation

Read data from a web address - process - write to a web address



http://myhost.com/algorithm/neuralnetwork

http://myhost.com/dataset/trainingset1

http://myhost.com/model/predictivemodel1

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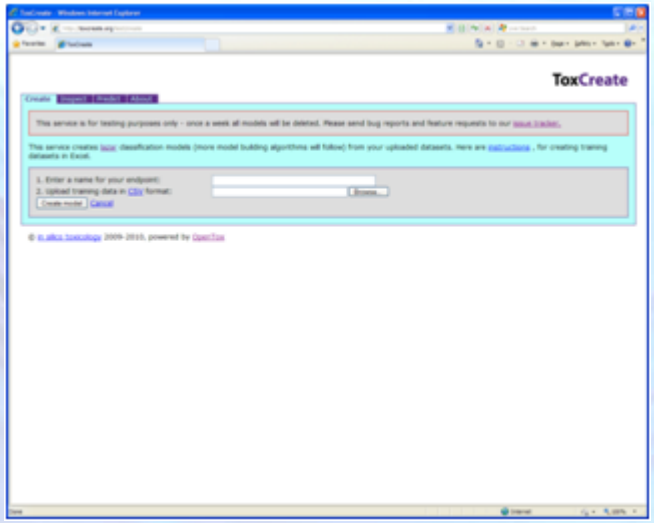
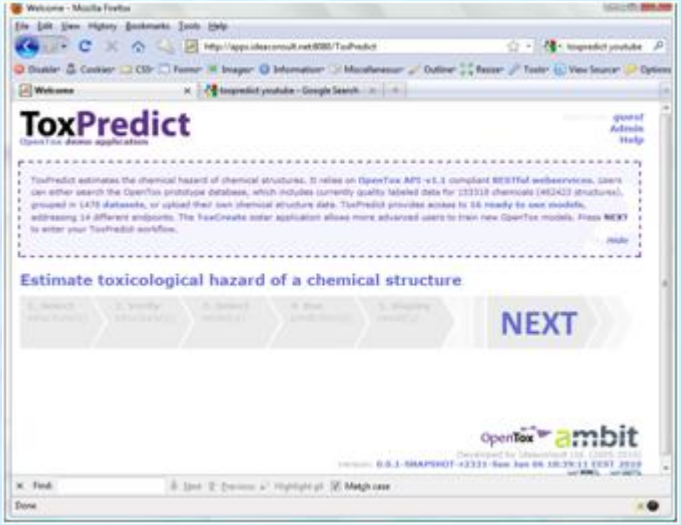
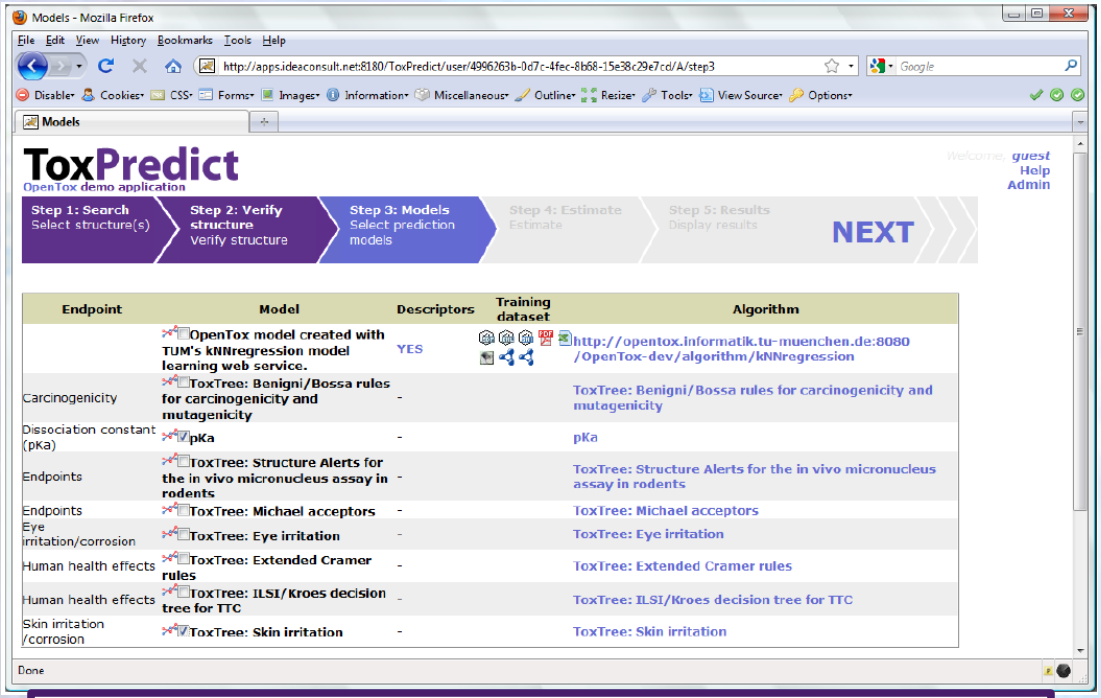
Prototype applications

- Two end user oriented demo applications, making use of OpenTox webservices, have been developed, deployed and are available for testing – toxcreate.org and toxpredict.org
- ToxCreate creates models from user supplied datasets
- ToxPredict uses existing OpenTox models to estimate chemical compound properties





What you can do with it …



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

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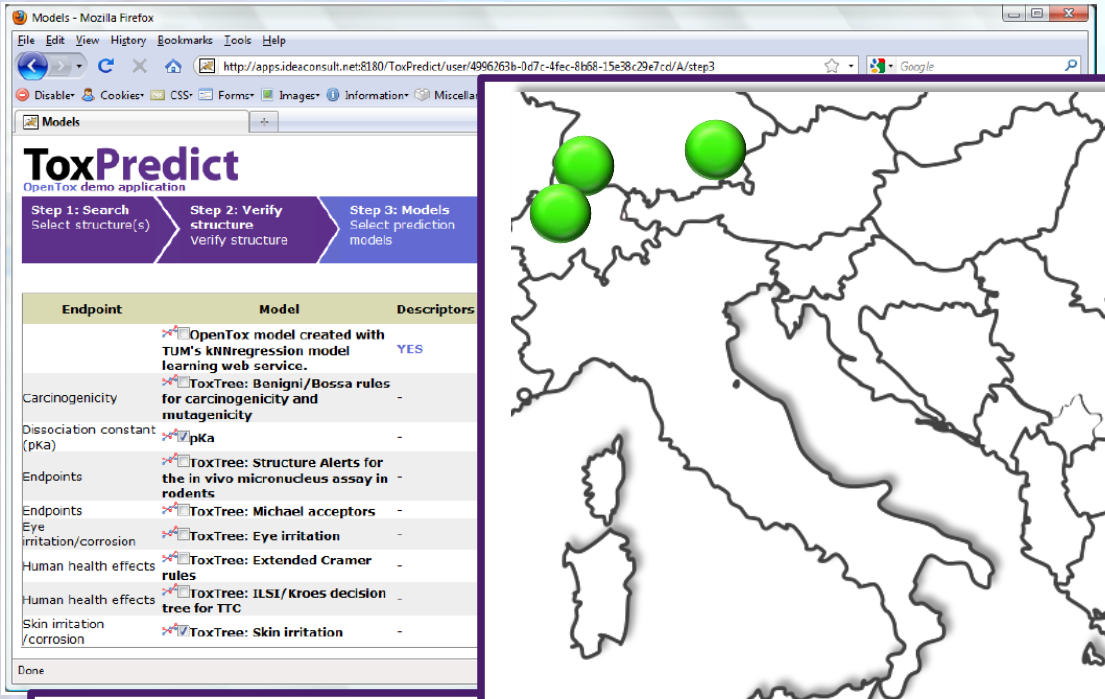
What you can do with it …



Simple building c

applications

methods and

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

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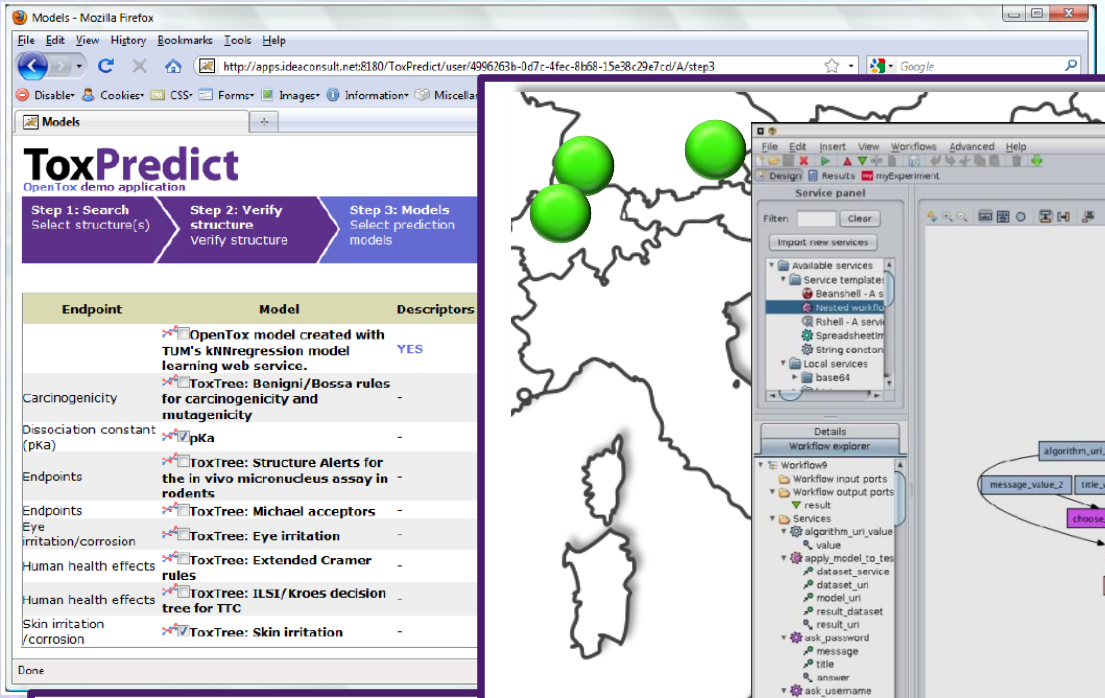
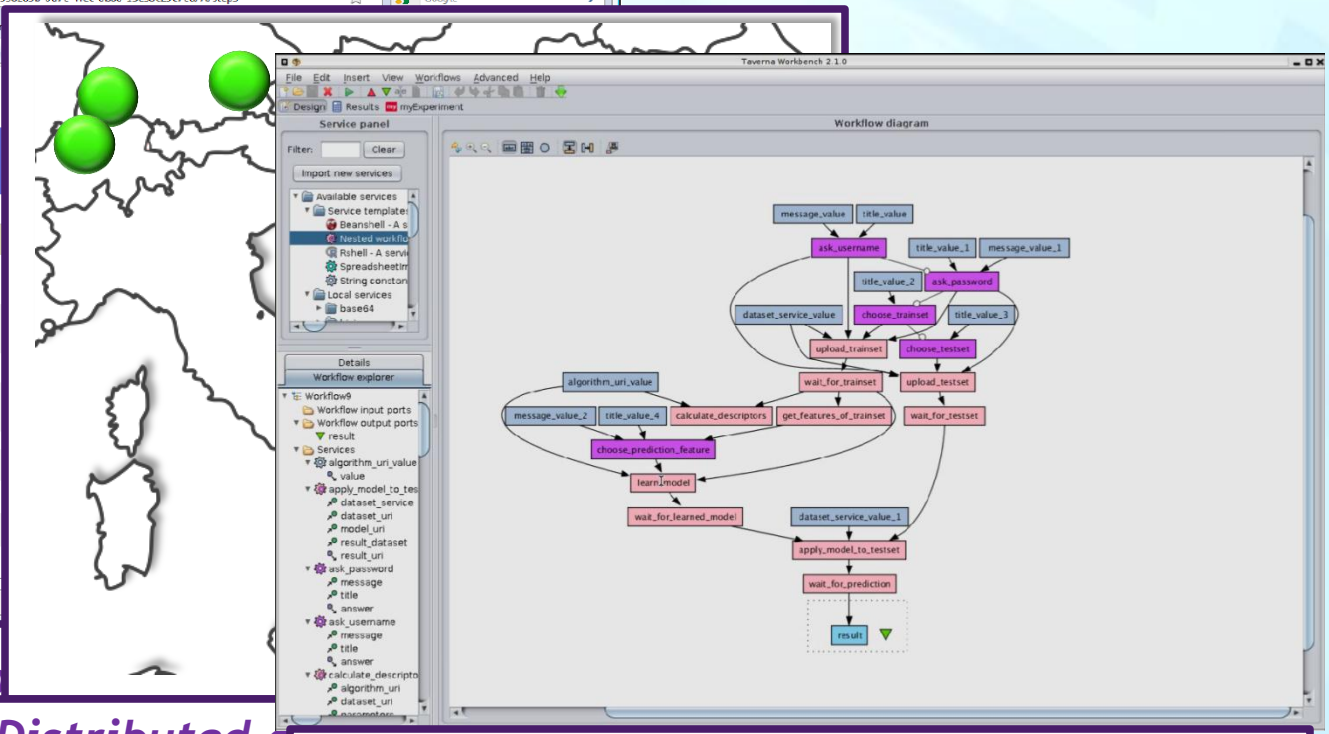
What you can do with it …





Simple building applications methods and

Distributed wide range methods

Integration into workflow systems for computational biology

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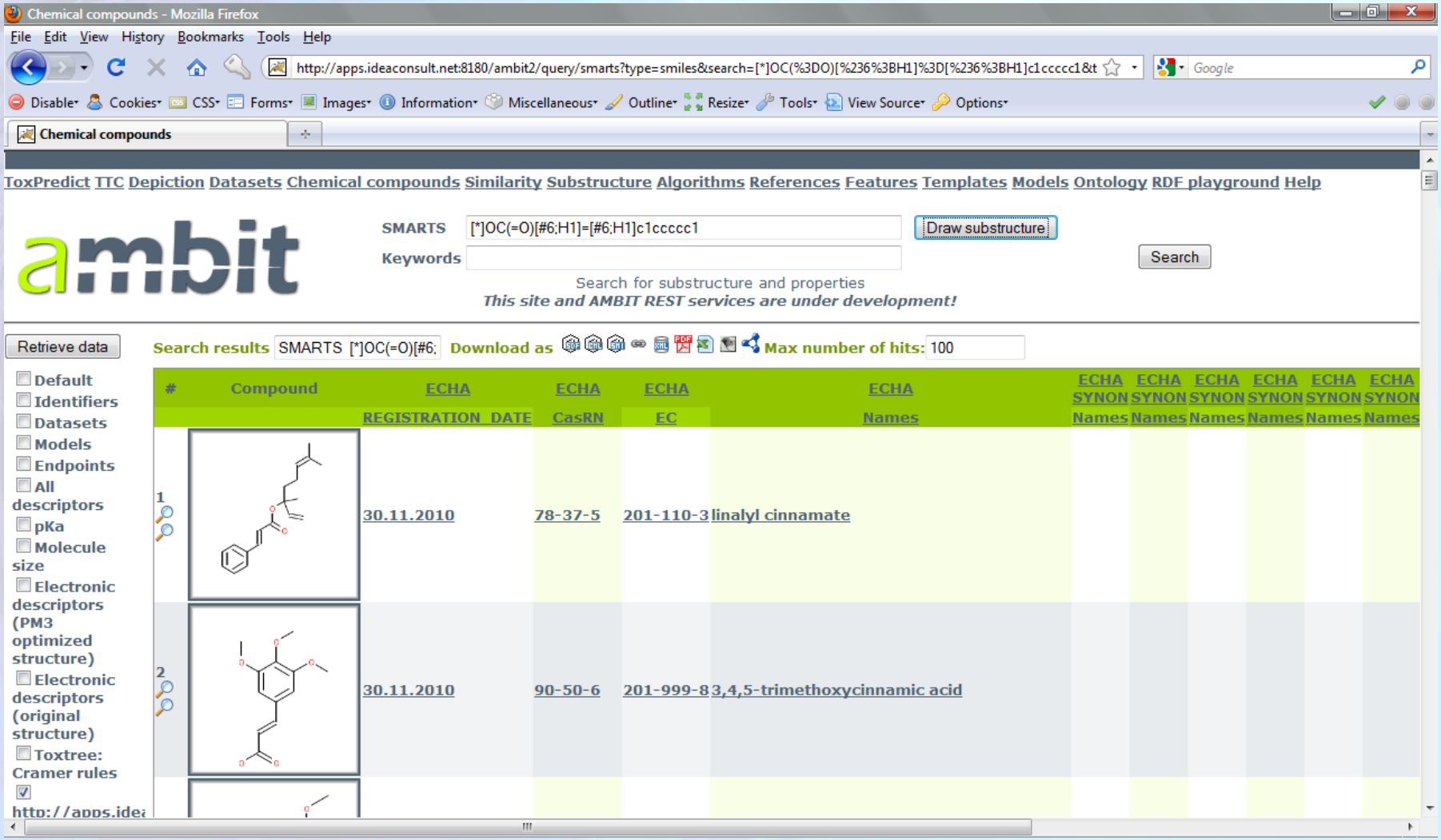
OpenTox: Databases



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Interoperability & Vocabulary

- Dogs
  - Collie
  - Labrador
- Cats
  - Siamese
  - Persian
- Birds
  - Sparrow
  - Owl

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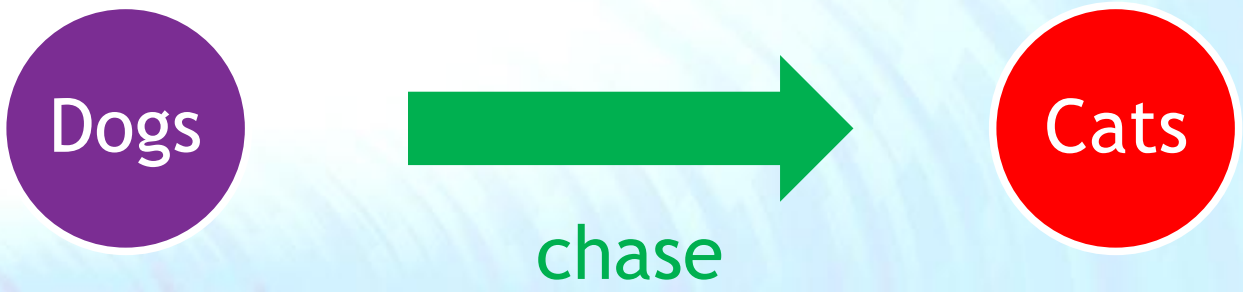
Interoperability & Vocabulary



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Interoperability & Ontology

Org A

Collie

chase

Siamese

Org B

Collie

Siamese

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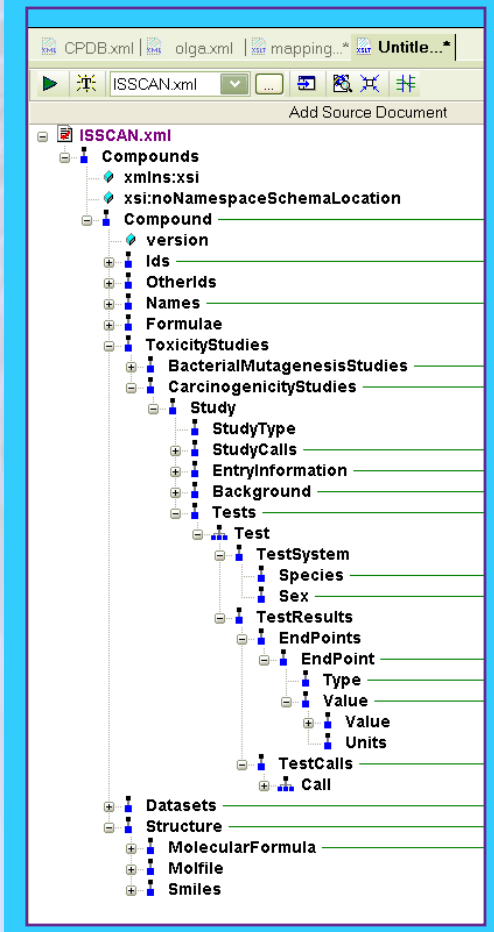
Toxicological Endpoint Ontology Development

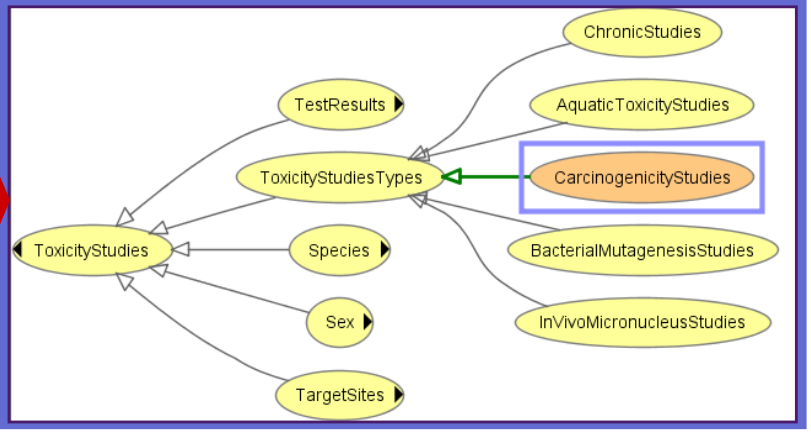
ToxML schema



Other publicly available resources:
DSSTox, GoReni (ITEM), ISSCAN ...

OpenTox Toxicological Endpoint Ontology

Ontology Development

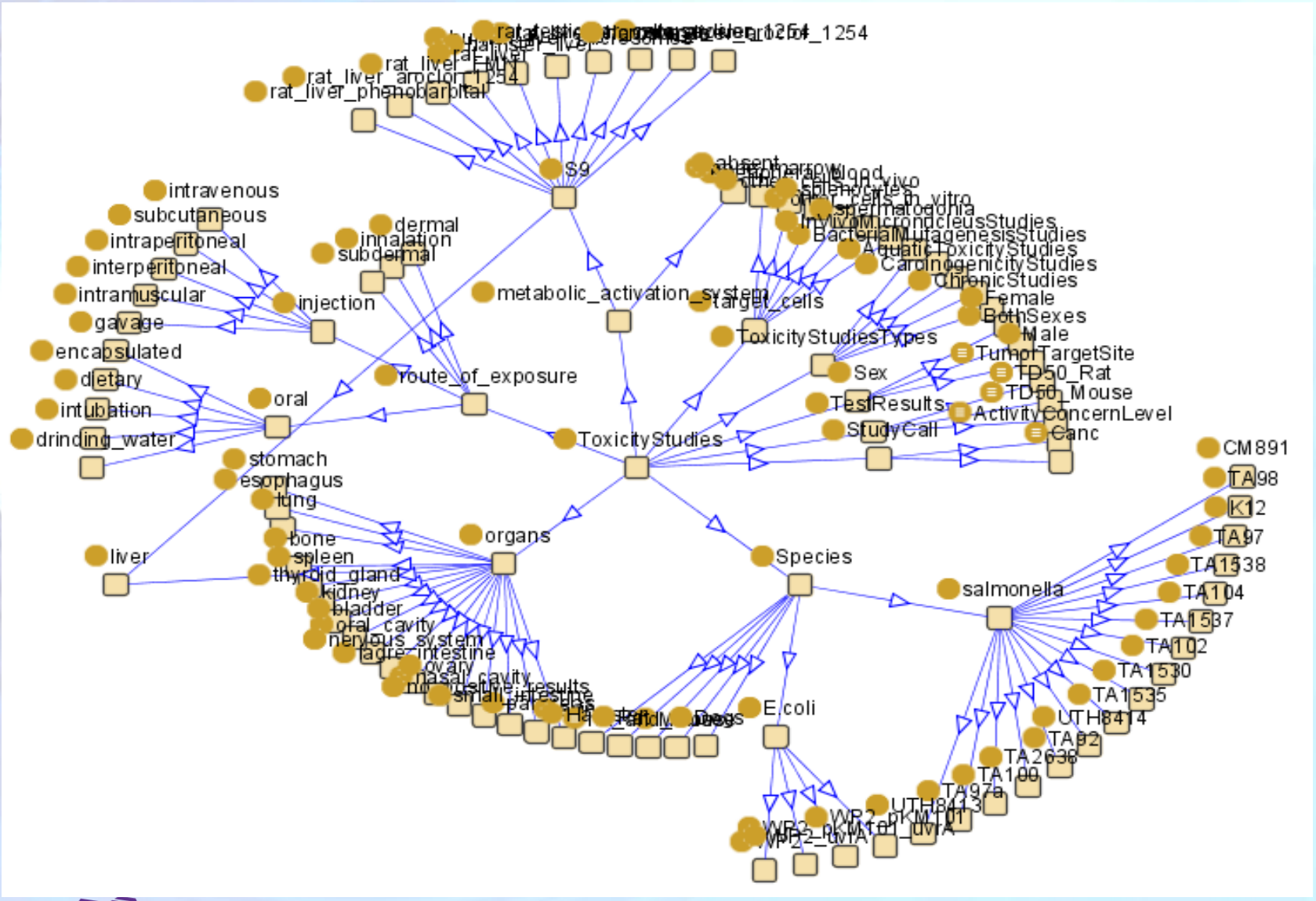


Collaborative Protégé Environment

Re-use of terms defined in neighbouring ontologies (e.g. OBO)

OpenTox

Toxicological Ontology: graphical representation



OpenTox

Need for communications in the community overcoming different languages and vocabularies

Explaining the rules of different games on a conservation project trip in the Caprivi, Namibia

From Conservation Project Trip in Caprivi Delta

OpenTox

OpenToxipedia

OpenTox

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OpenToxipedia

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

OpenTox Community Resource for Toxicology Vocabulary and Ontology

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

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

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

Guidance for Vocabulary Resource entries

www.opentox.org/opentoxipedia

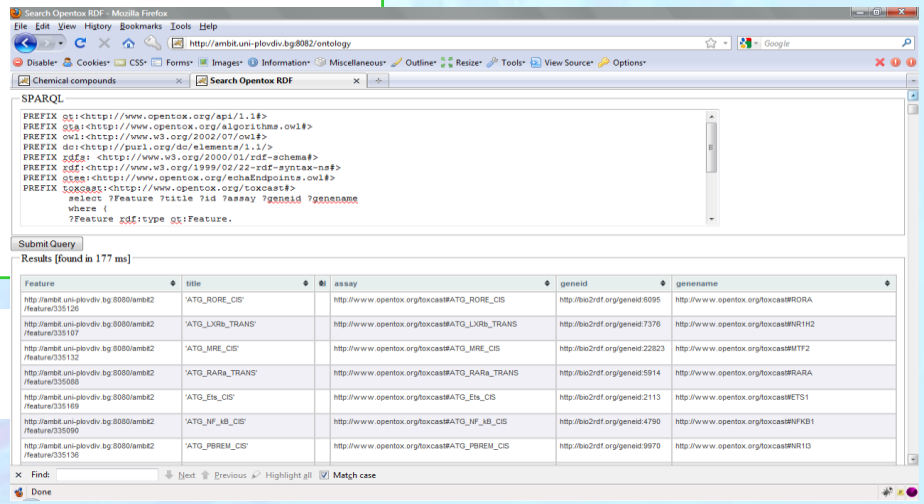
OpenTox

Dataset and Ontology - find an assay, linked to specific gene

```
PREFIX ot:<http://www.opentox.org/api/1.1#>
PREFIX ota:<http://www.opentox.org/algorithms.owl#>
PREFIX owl:<http://www.w3.org/2002/07/owl#>
PREFIX dc:<http://purl.org/dc/elements/1.1/>
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#>
PREFIX rdf:<http://www.w3.org/1999/02/22-rdf-syntax-ns#>
PREFIX otee:<http://www.opentox.org/echaEndpoints.owl#>
PREFIX toxcast:<http://www.opentox.org/toxcast#>
                select ?Feature ?title ?id ?assay ?geneid ?genename
                where {
                ?Feature rdf:type ot:Feature.
  {?Feature dc:title ?title}.
  {?Feature owl:sameAs ?assay}.
  {?assay toxcast:gene ?geneid}.
  {?assay toxcast:hasProperty ?genename}.
  {?genename rdf:type toxcast:GENE_NAME}.

                }
```

http://ambit.uni-plovdiv.bg:8080/ambit2/dataset/961?feature_uris[]=http://ambit.uni-plovdiv.bg:8080/ambit2/feature/335126



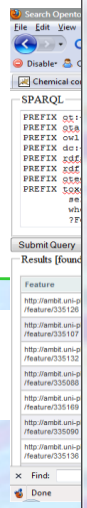
Query an OpenTox ontology service at http://ambit.uni-plovdiv.bg:8082/ontology

OpenTox

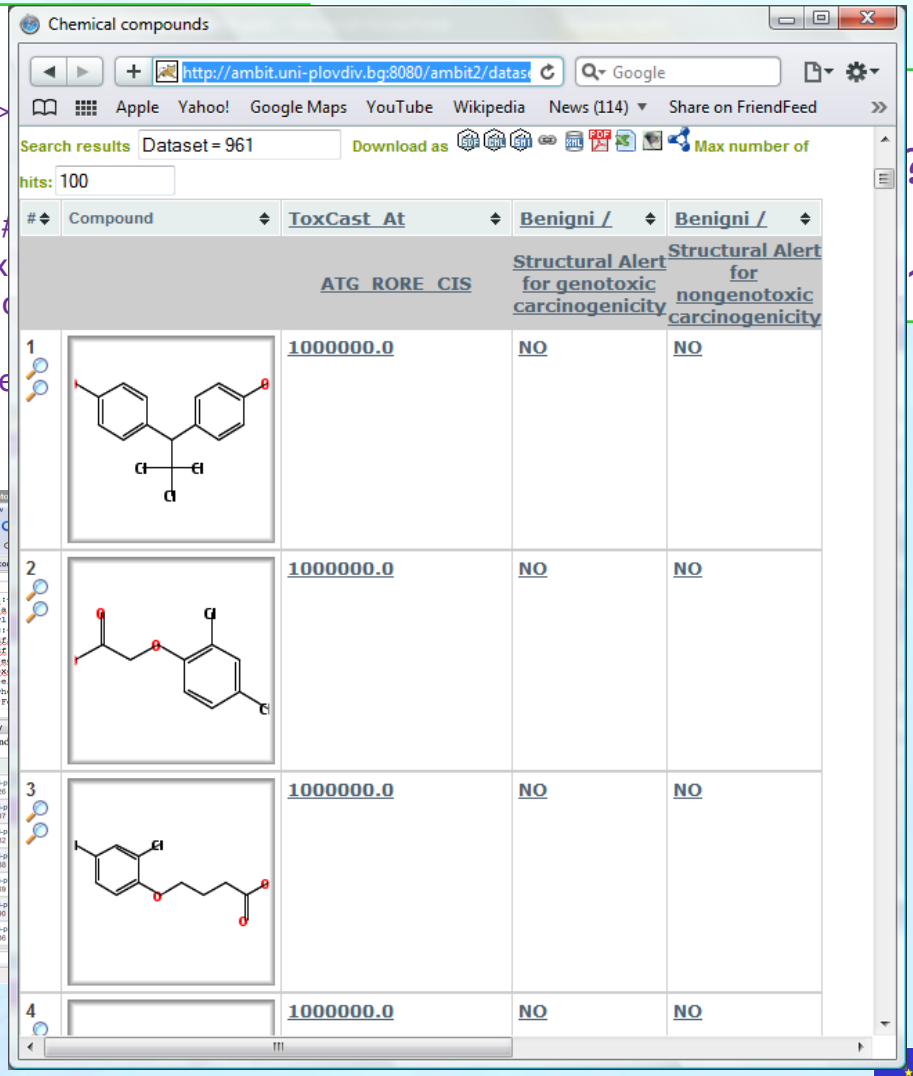
Dataset and Ontology - find an assay, linked to specific gene

```
PREFIX ot:<http://www.opentox.org/api/1.1#>
PREFIX ota:<http://www.opentox.org/algorithms.owl#>
PREFIX owl:<http://www.w3.org/2002/07/owl#>
PREFIX dc:<http://purl.org/dc/elements/1.1/>
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#
PREFIX rdf:<http://www.w3.org/1999/02/22-rdf-syntax
PREFIX otee:<http://www.opentox.org/echaEndpoints.
PREFIX toxcast:<http://www.opentox.org/toxcast#>
                select ?Feature ?title ?id ?assay ?geneid ?ge
                where {
                ?Feature rdf:type ot:Feature.
  {?Feature dc:title ?title}.
  {?Feature owl:sameAs ?assay}.
  {?assay toxcast:gene ?geneid}.
  {?assay toxcast:hasProperty ?genename}.
  {?genename rdf:type toxcast:GENE_NAME}.

                }
```



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



?feat

126

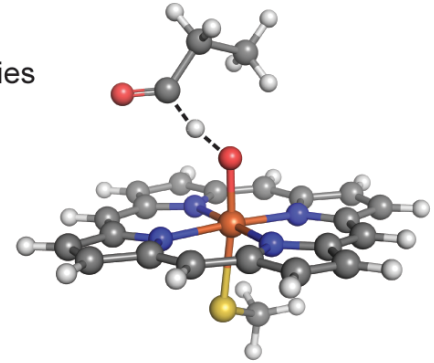
OpenTox

SMARTCyp Service for Predicting Metabolites

Atom Reactivity Library

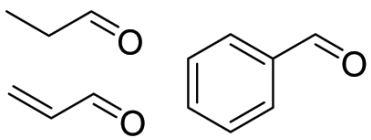
A. Calculate Quantum Chemical Reference Energies

Calculate transition state energies using density functional theory



B. Define SMARTS Rules

Group calculations by fragments and calculate average energies



[CX3H1](=O)[#6]

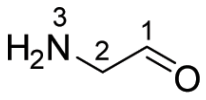
40.2 kJ/mol

SMARTCyp - developed by Patrik Rydberg, University of Copenhagen

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

SMARTCyp

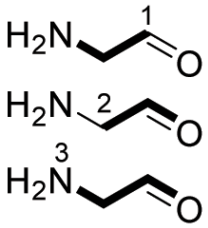
1. Assign Energies By SMARTS matching



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

$A_i = Maxbonds_i / Maxbonds_{all}$



$A_1 = 2 / 3 = 0.67$

$A_2 = 2 / 3 = 0.67$

$A_3 = 3 / 3 = 1.00$

3. Compute Score and Rank Atoms

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

$S_1 = 40.2 - 8*0.67 = 34.84$

$S_2 = 39.8 - 8*0.67 = 34.44$

$S_3 = 54.1 - 8*1.00 = 46.10$

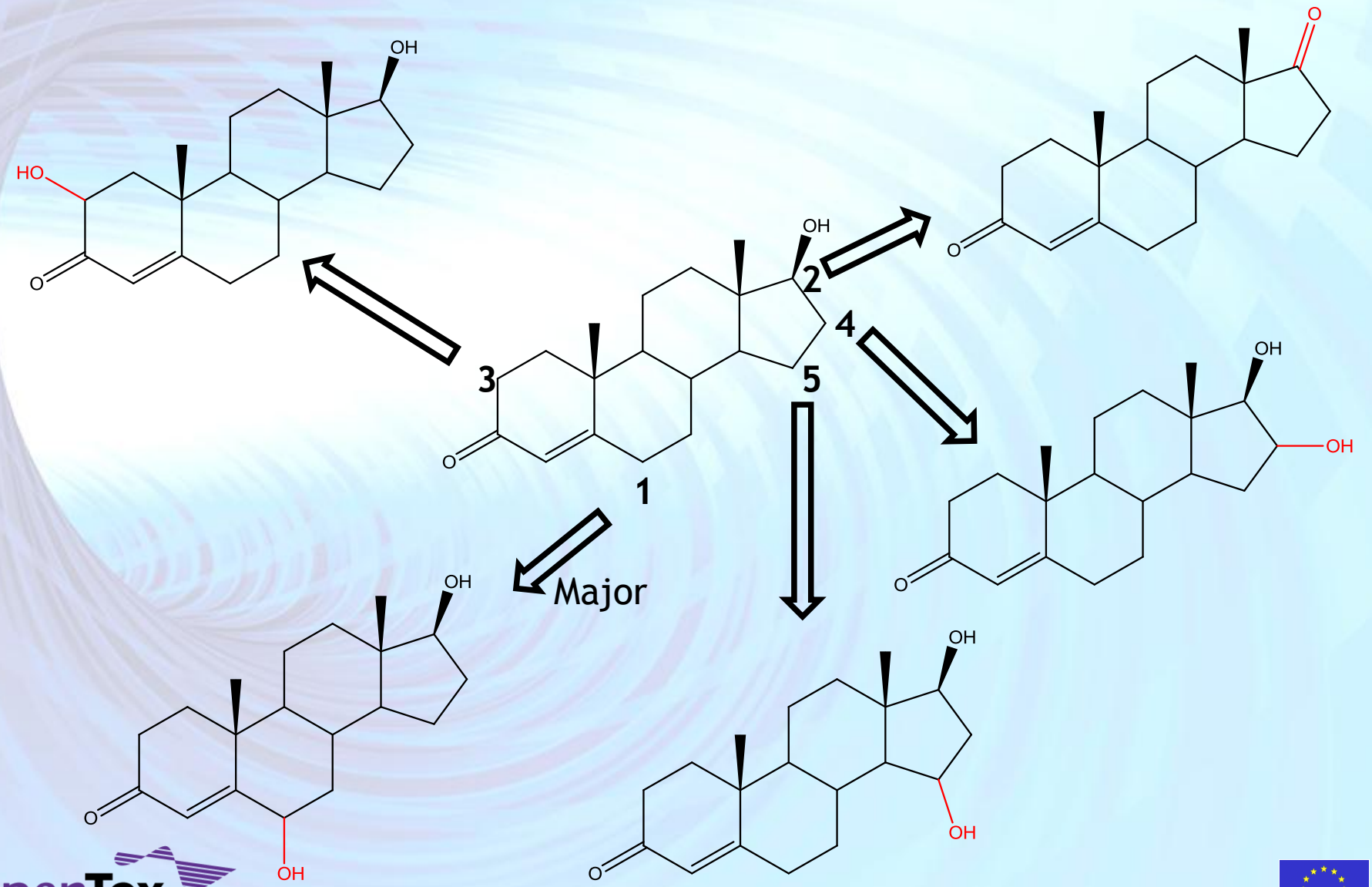
Atom 1 - Rank 2

Atom 2 - Rank 1

Atom 3 - Rank 3

OpenTox

SmartCYP Prediction of Testosterone Metabolites

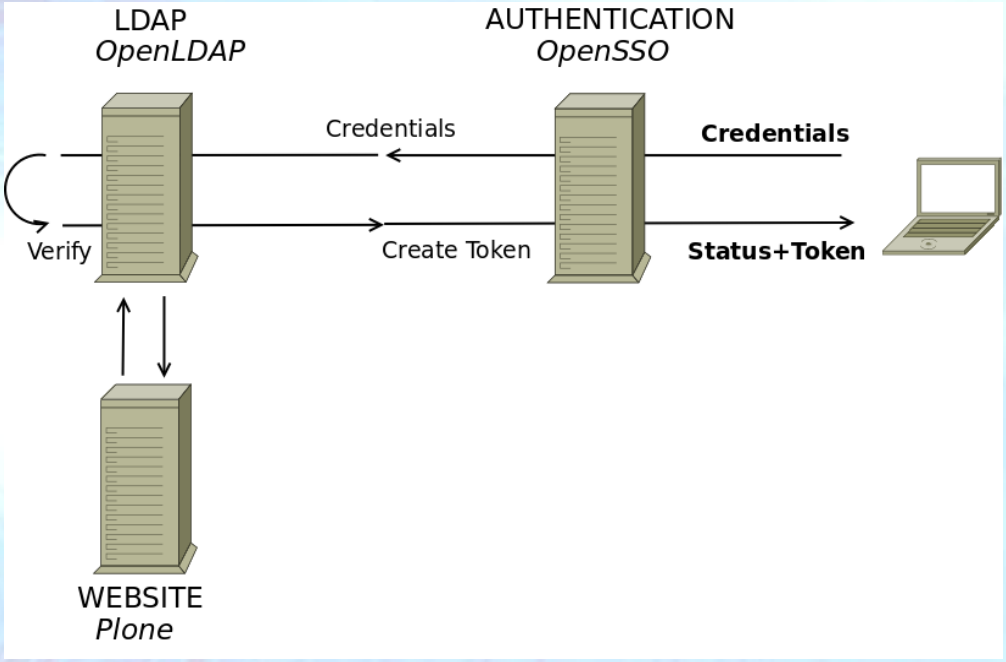


OpenTox

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

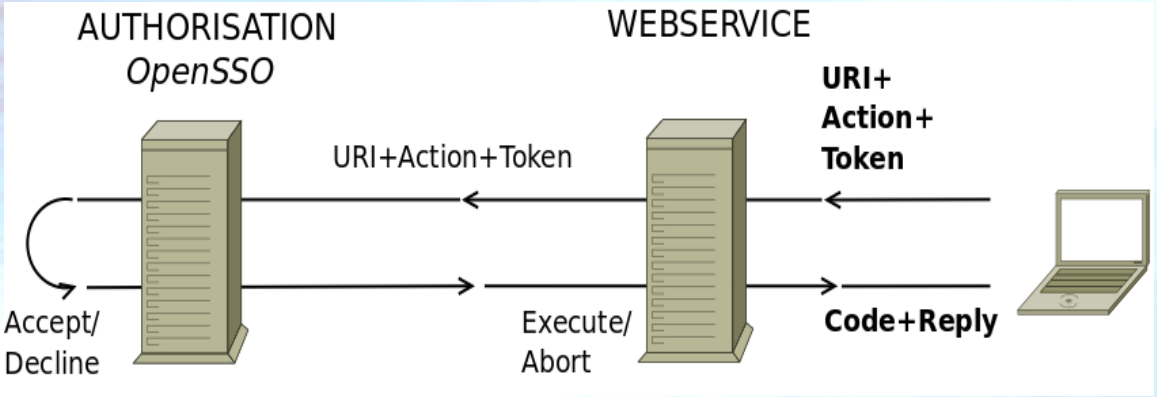
Authentication



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

OpenTox

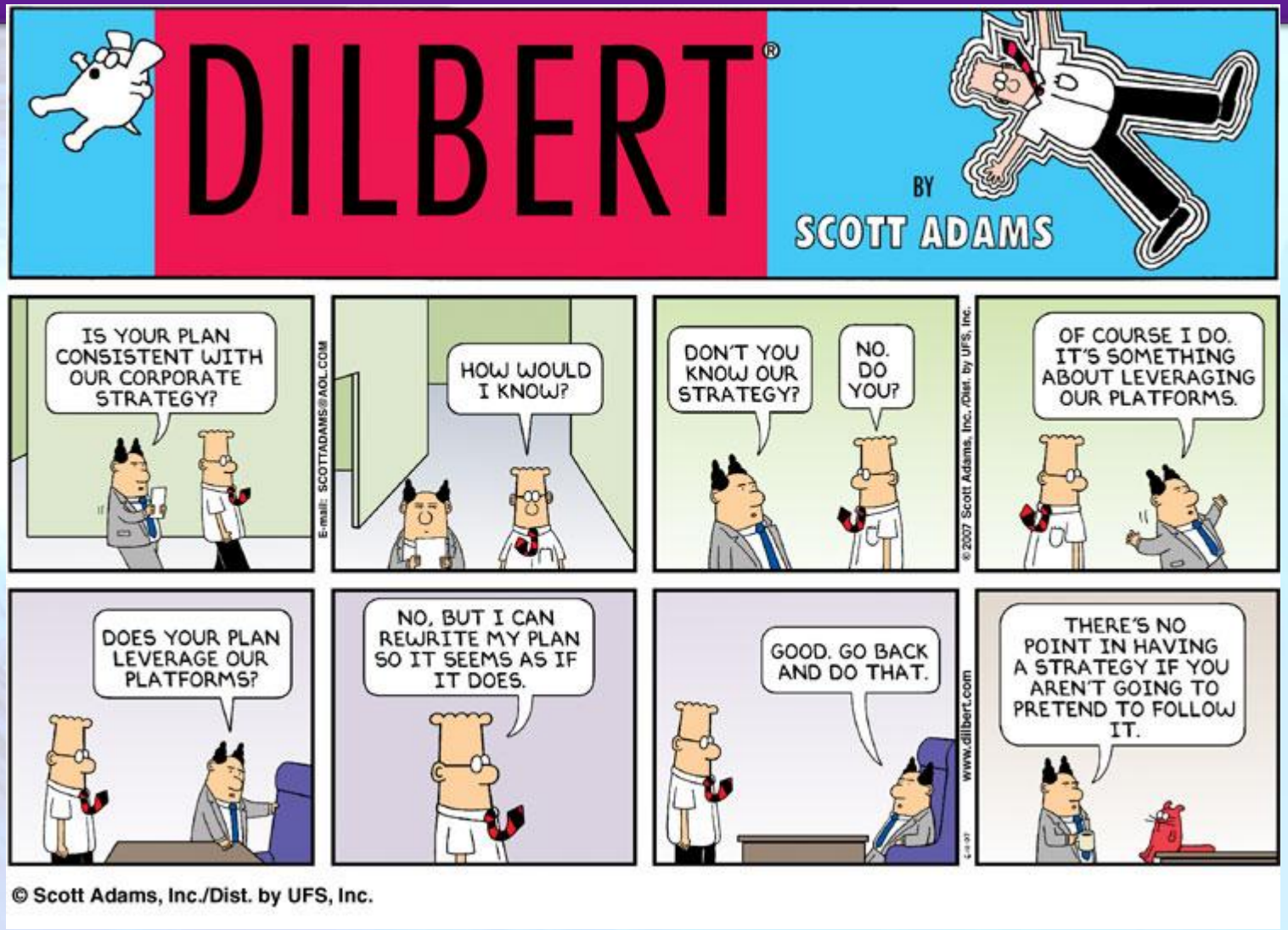
Authorisation



- 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

OpenTox

OpenTox Adoption



OpenTox

OpenTox - Bioclipse

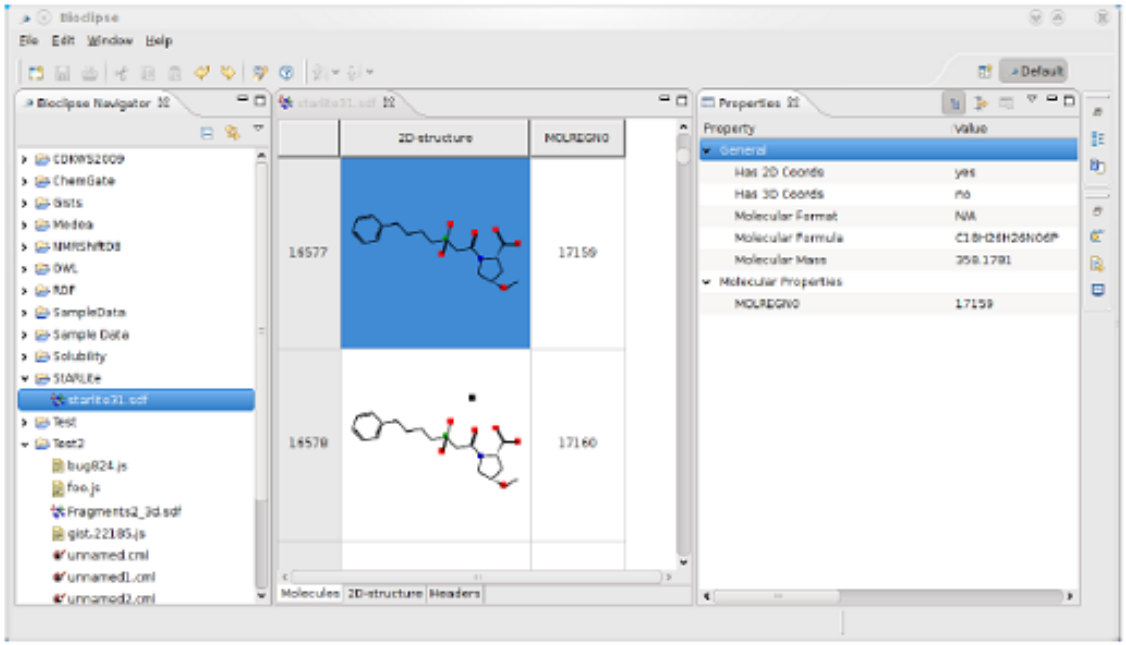
UPPSALA UNIVERSITET

Problem

Building Blocks

Conclusion

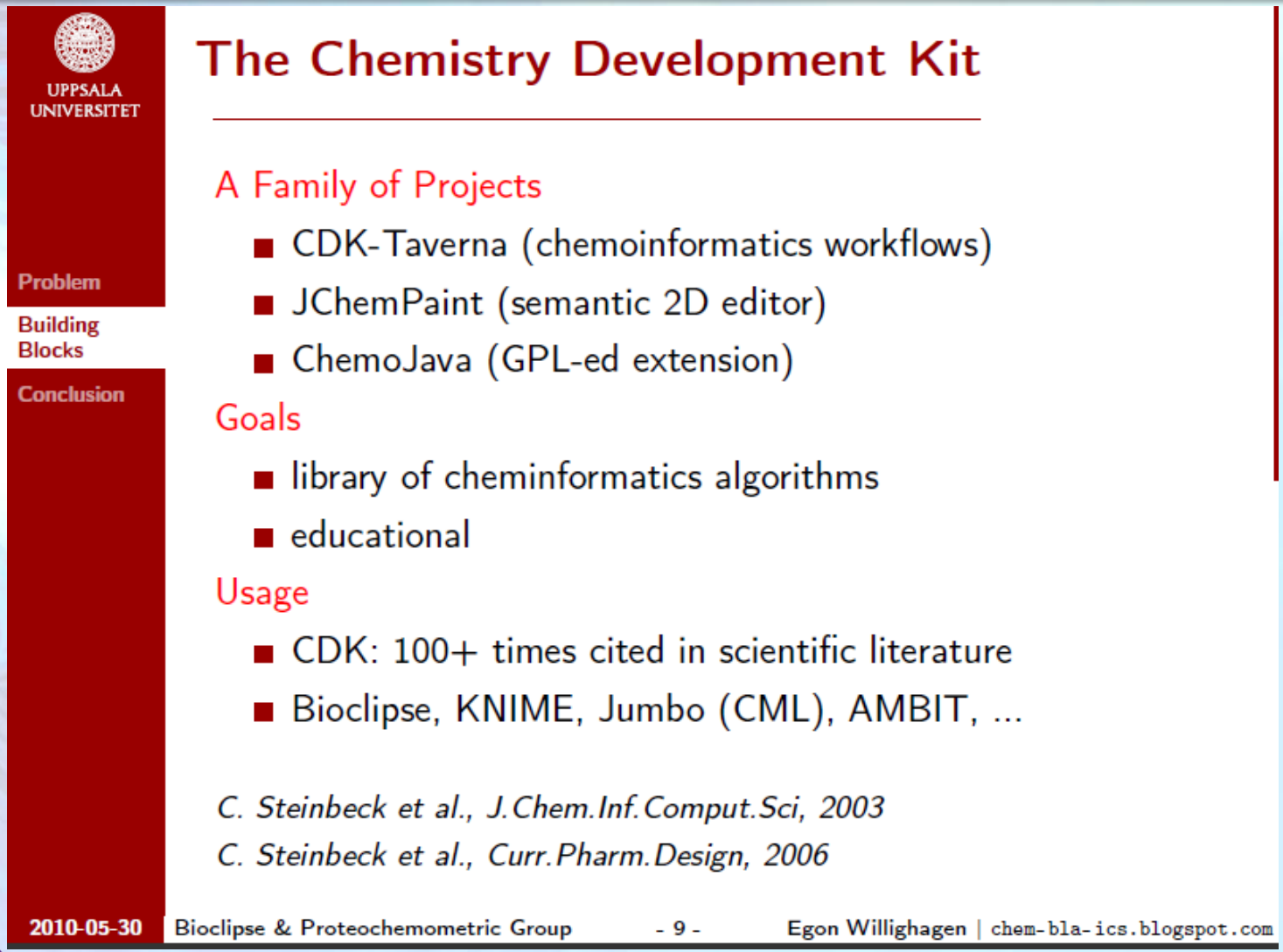
Bioclipse



O. Spjuth et al., BMC Bioinformatics 2007, 8:59

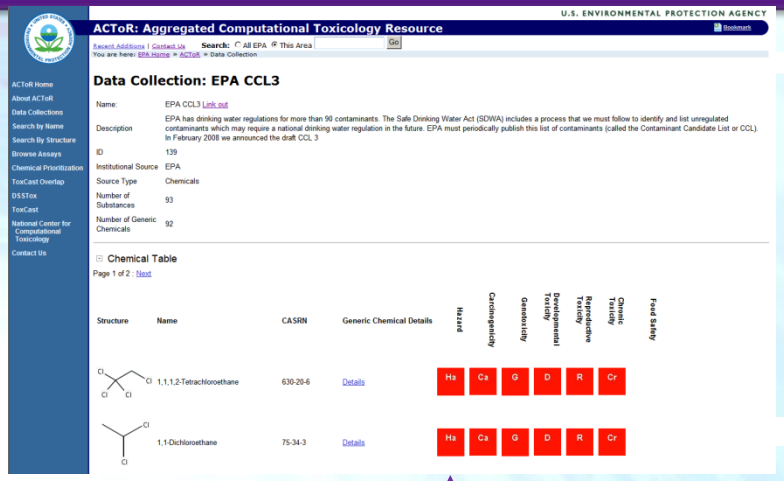
OpenTox

OpenTox - CDK



OpenTox

OpenTox - ToxCast



ACToR Web Browser

ACToR API

Chemical

Chemical ID, Structure

Targeted Testing

Assay

Tabular Data, Links to Web Resources

ToxRefDB

...

DevToxDB

Specialized Toxicology Databases

Genomics

MicroArray Data

BioRefDB

Biological Reference Data

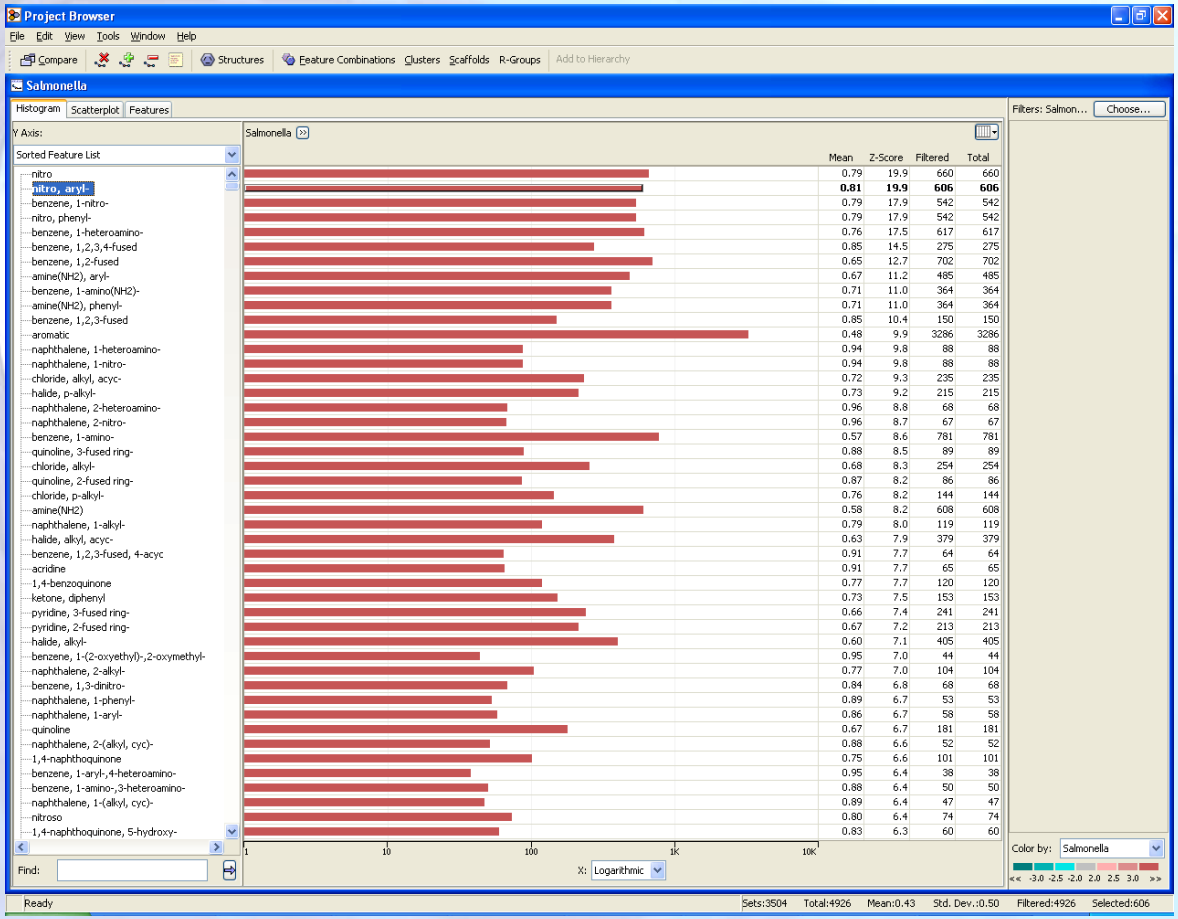
ToxMiner

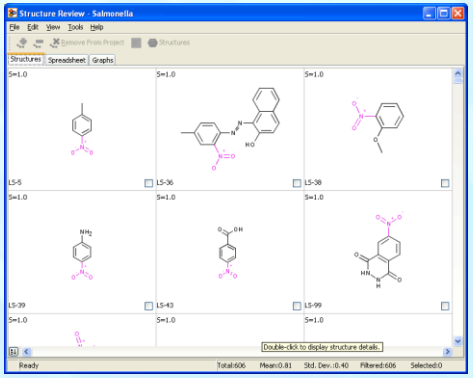
Data Mining

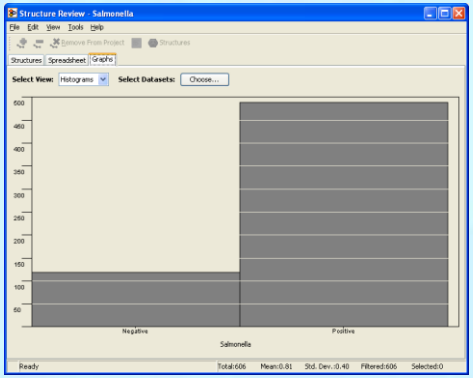
Internet Searches

http://actor.epa.gov/

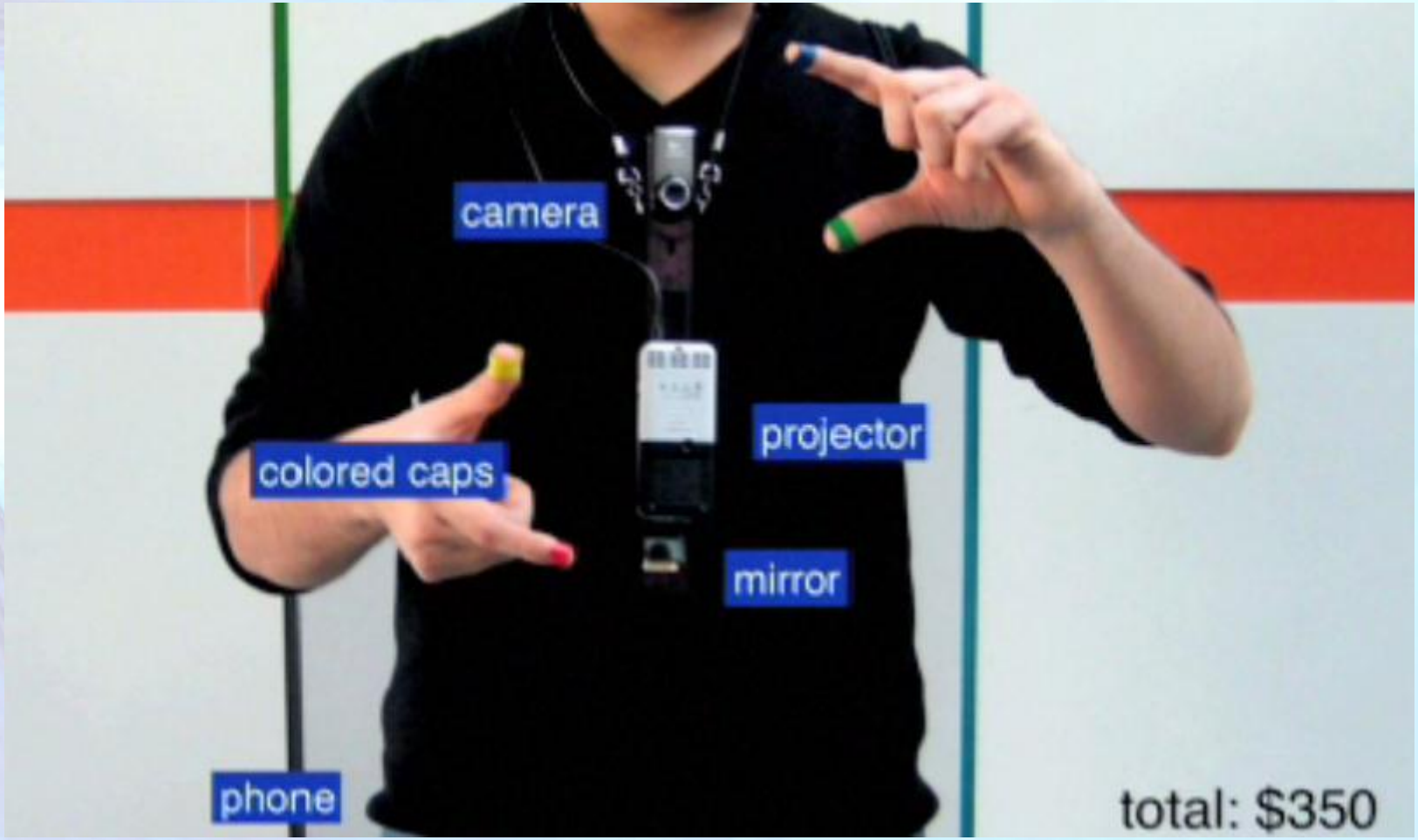
OpenTox - Leadscope







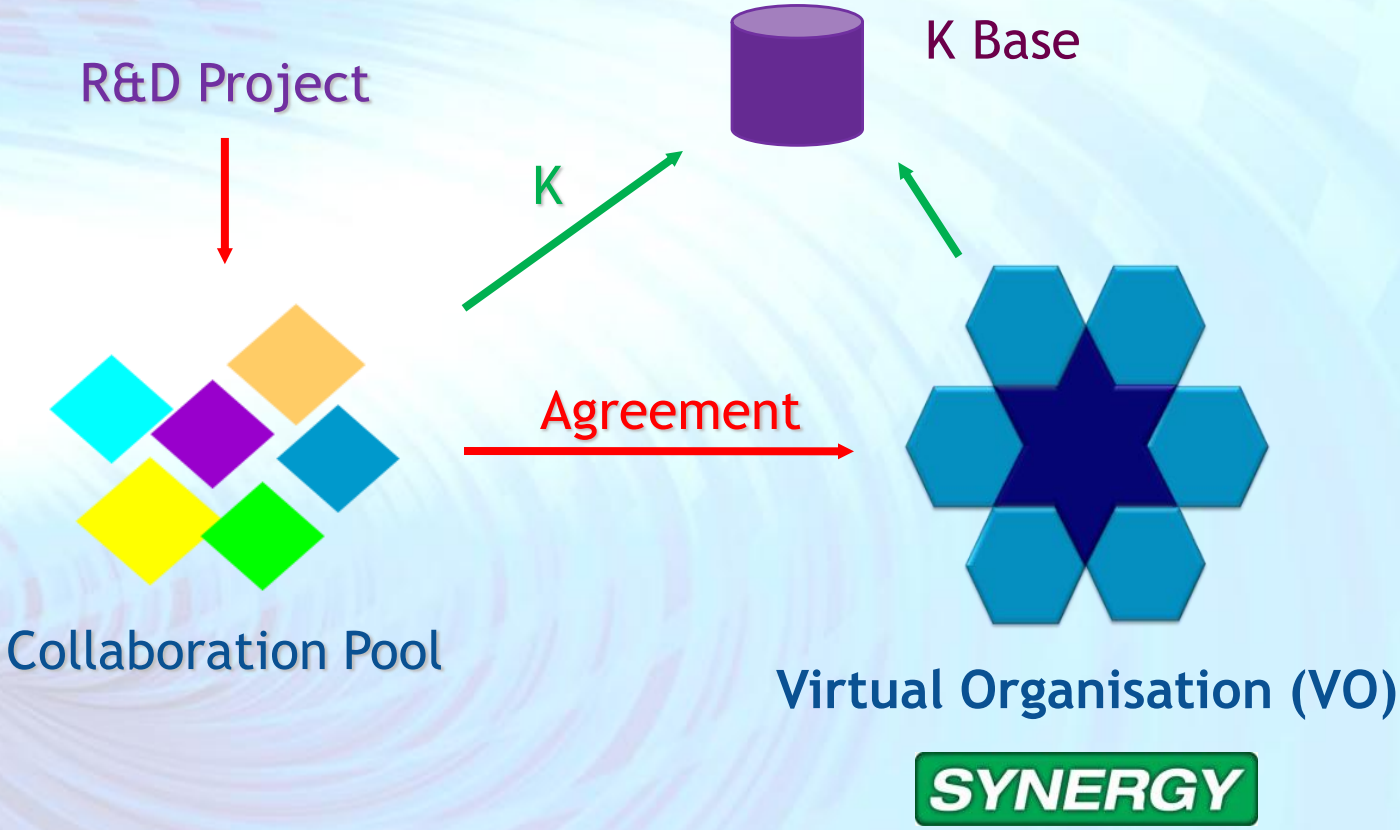
Augmented Reality



Processing Packaging Information

OpenTox

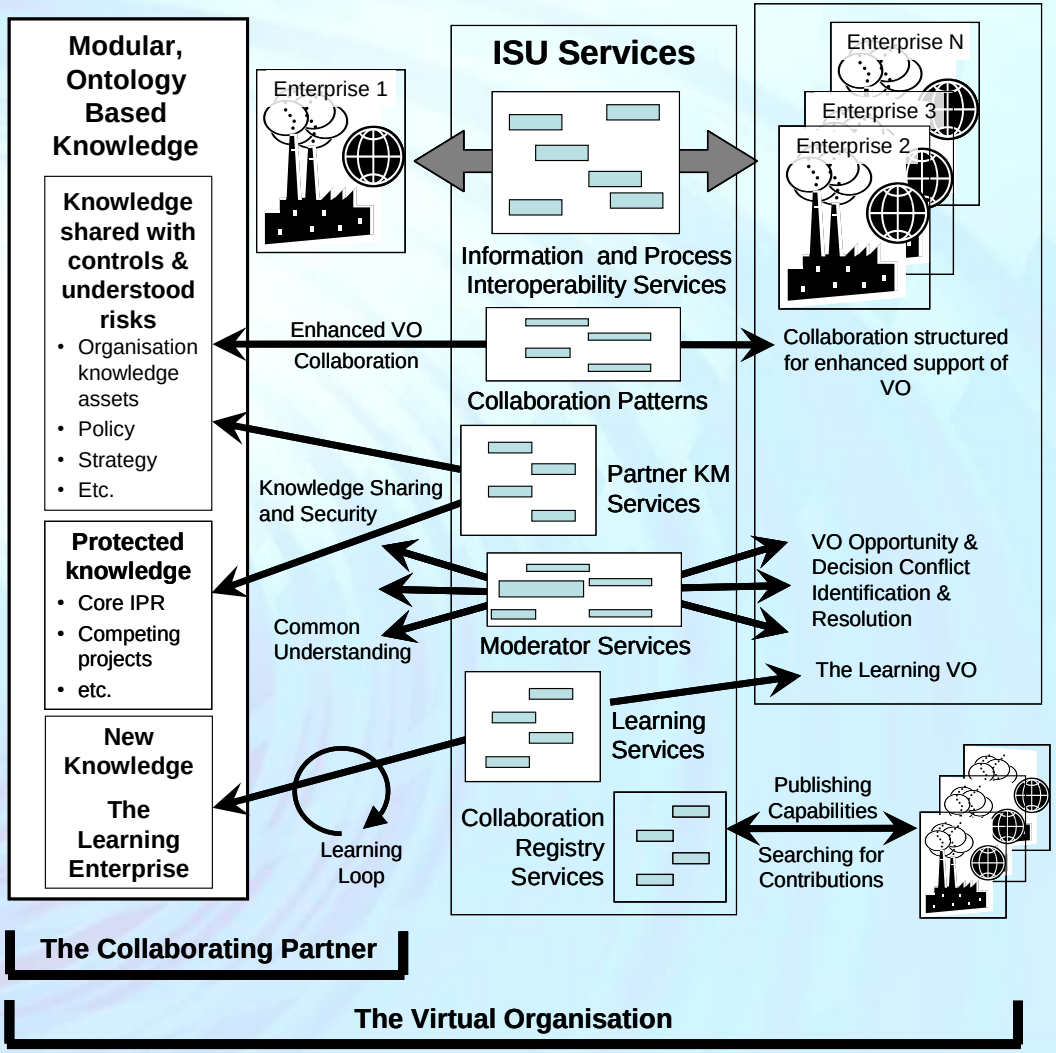
Virtual Organisation Pilots



OpenTox

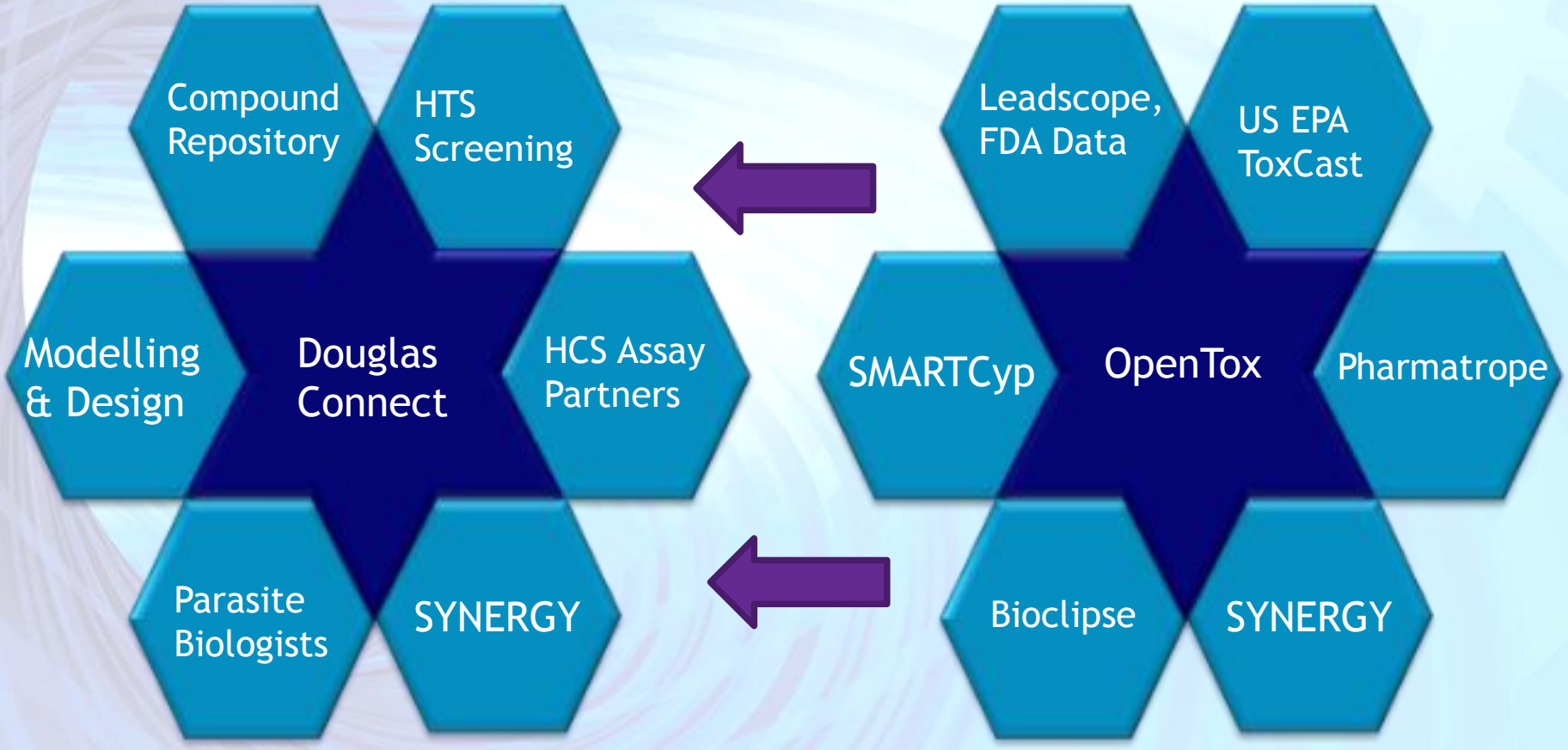
SYNERGY Collaboration Services for VOs

SYNERGY website:
www.synergy-ist.eu/



OpenTox

Virtual Organisation Pilots



Neglected Disease Drug Design VO

Predictive Toxicology VO

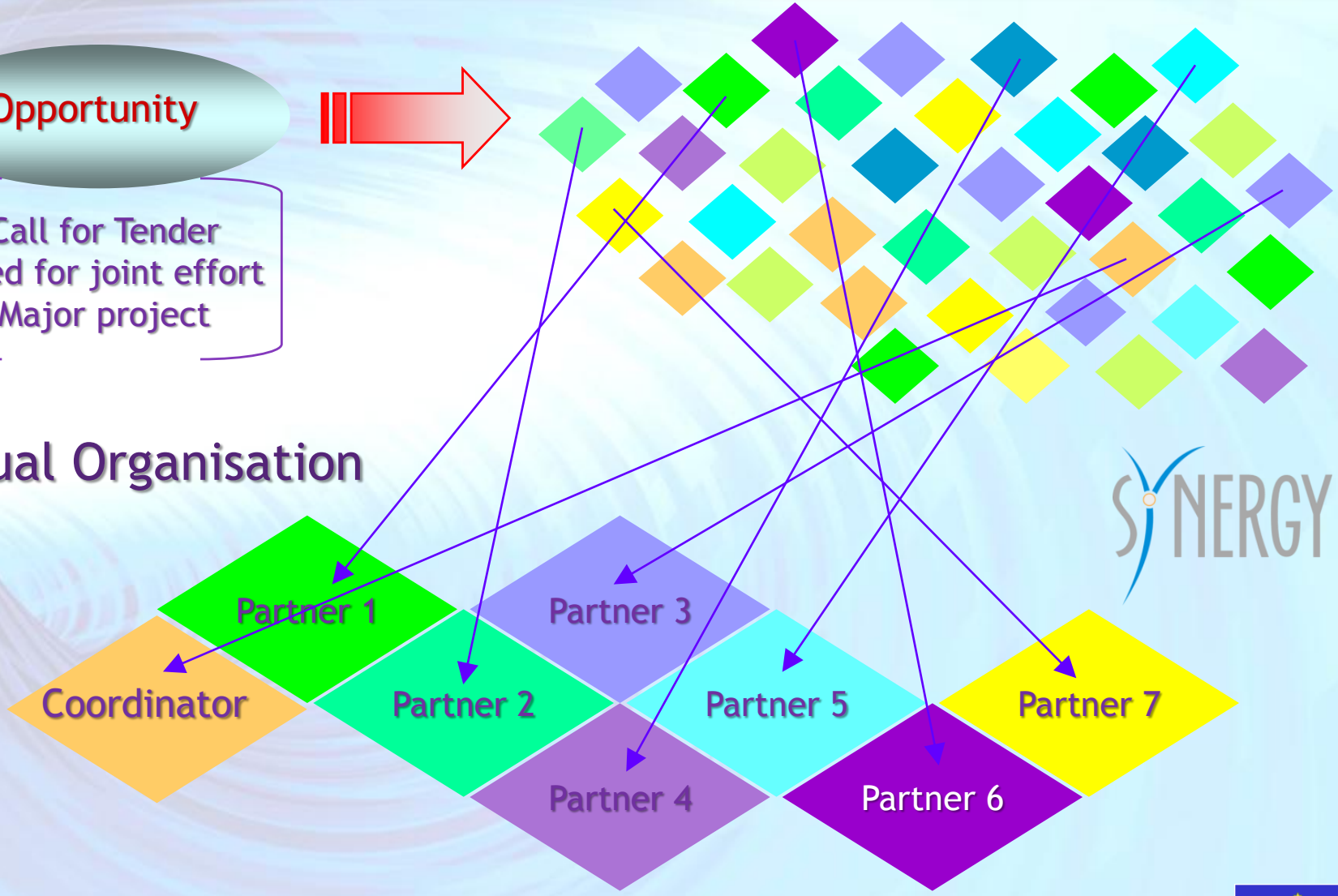
OpenTox

Creation of VO from Collaboration Pool

Network

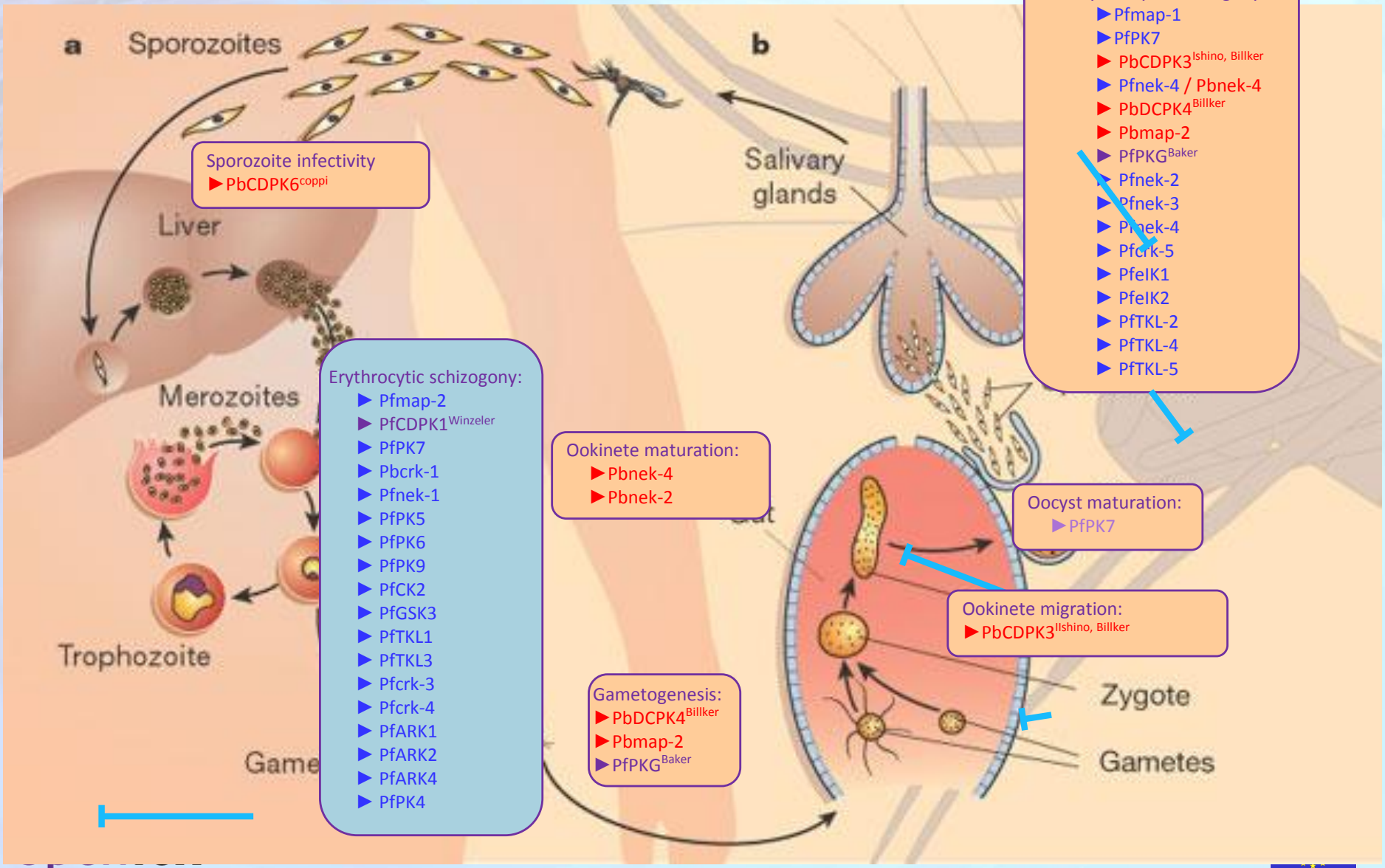
Opportunity

Call for Tender
Need for joint effort
Major project

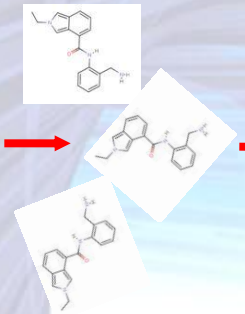


OpenTox

SAM VO targeting Plasmodium Kinases

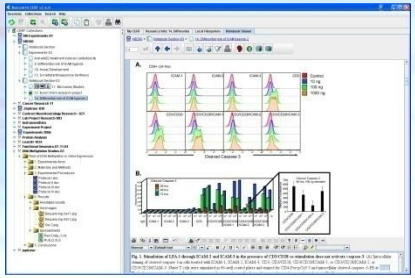


Synergy Drug Design Collaboration Pilot

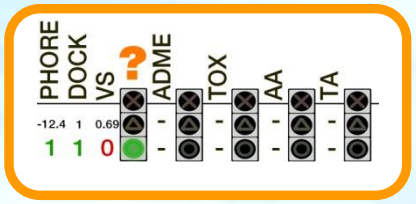


Screened Library

Data

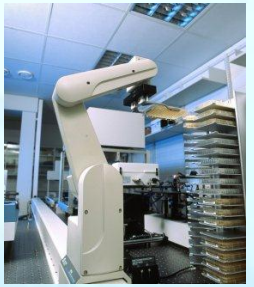


CERF

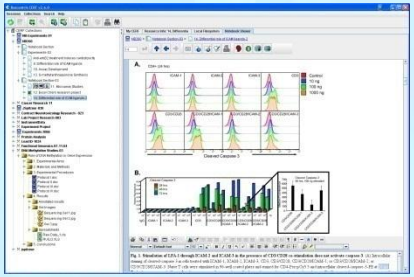


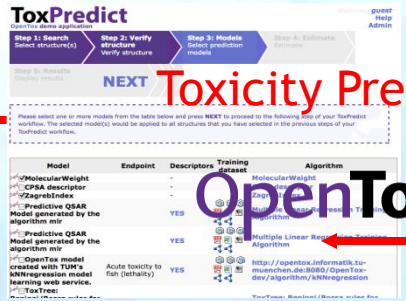
Refine Predictions

SYNERGY



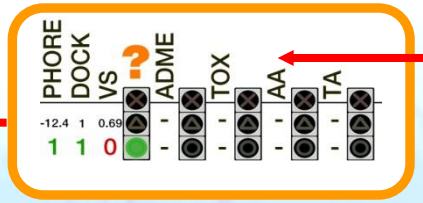
Data



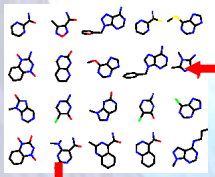


Toxicity Predictions

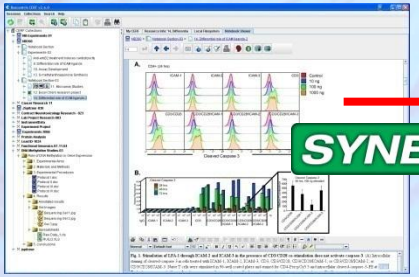
OpenTox



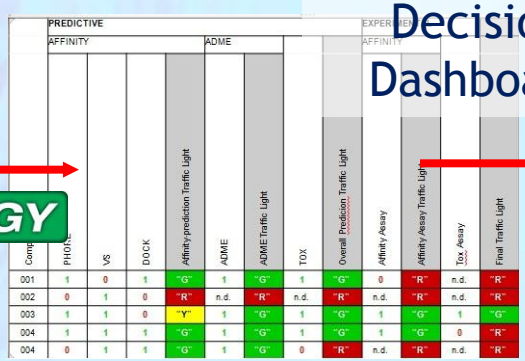
SYNERGY



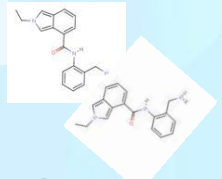
Toxicity Assays



SYNERGY



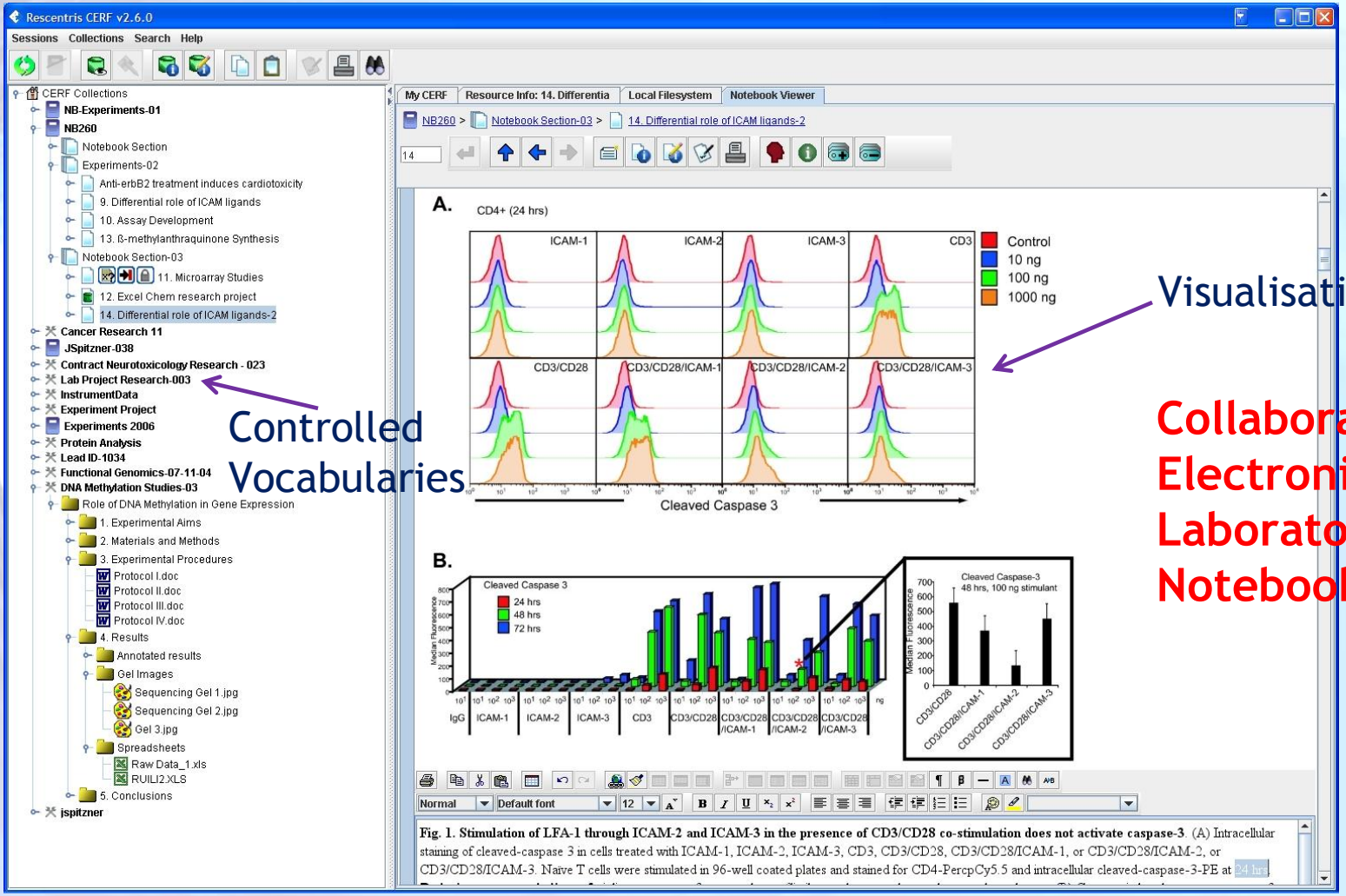
Decision Dashboard



(Safer) Drug Leads

OpenTox

Recording of Collaborative R&D



Controlled Vocabularies

Visualisation

Collaborative Electronic Laboratory Notebook (ELN)

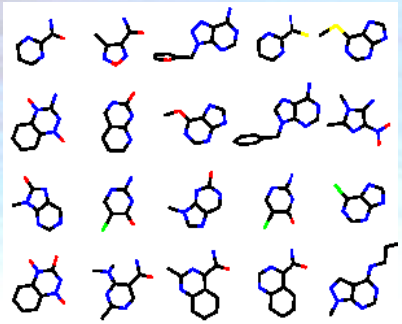
OpenTox

OpenTox - Synergy Predictive Toxicology VO Pilot Strategy Development & Case Study

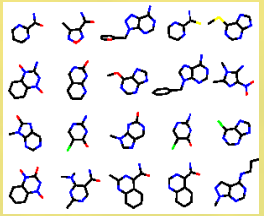
1. Data Mining of Human Adverse Drug Events
   - Data Mining of Literature Knowledge
2. Creation of Mechanism-based Hypothesis
   - Selection of Biological Pathways & Targets
3. Selection of Compounds
   - Prediction of Metabolites of Compounds
4. Selection of *in vitro* assays relevant to Mechanism
   - Selection and integration of Toxicity Data
5. Creation of Predictive Toxicology Model including Model Validation and Applicability Domain
6. Selection of Low and High Content Assays for Testing in Cell Lines
   - Analysis of Results

OpenTox

1. A library of compounds is entered to the ELN



ELN

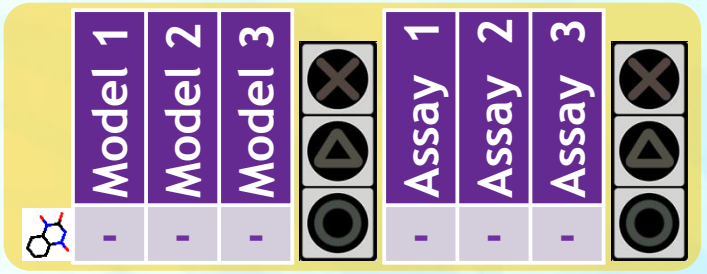


Synergy

OpenTox

2. Each compound is assigned a data structure in ELN

ELN

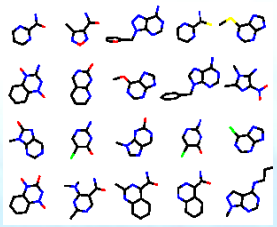


Synergy

OpenTox

OpenTox

3. ELN passes compounds to OpenTox and SYNERGY



ELN

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

Synergy

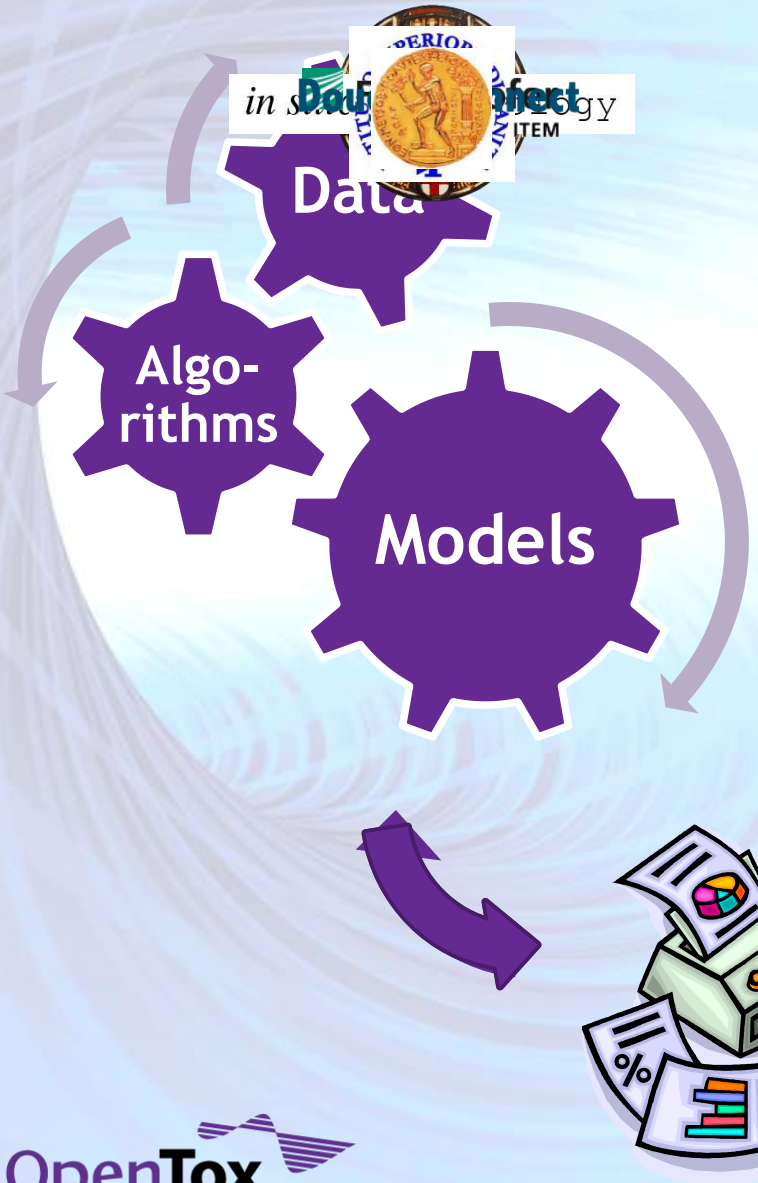
Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
-	-	-	-	-	-

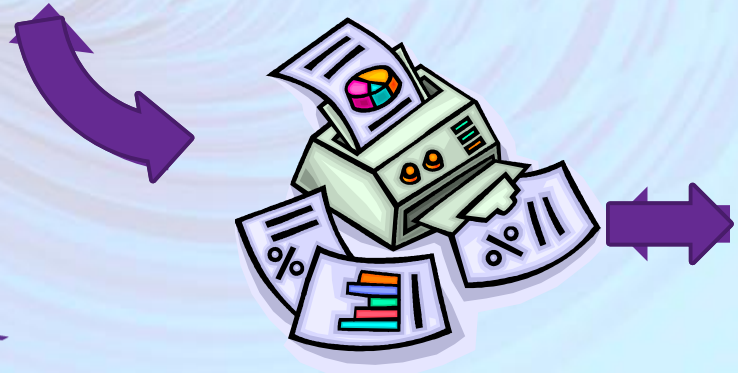
OpenTox

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

OpenTox

4. OpenTox computes toxicity predictions





ELN

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

Synergy

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

OpenTox

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

OpenTox

5. OpenTox sends back a report to ELN

ELN

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

Synergy

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

OpenTox

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

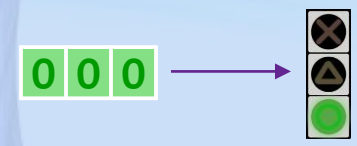
OpenTox

6. ELN sends the results to SYNERGY

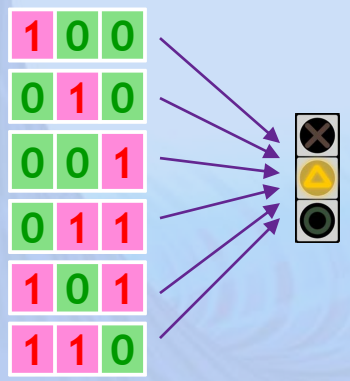
OpenTox

7. SYNERGY applies the Recommendation Rules

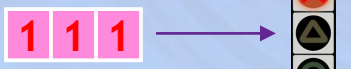
Recommendation Rules:



Non-toxic, high confidence



Inconclusive results, further study needed



Toxic, high confidence

ELN

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

Synergy

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

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8. Inconclusive data → SYNERGY calls a meeting

?

ELN

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

Synergy

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

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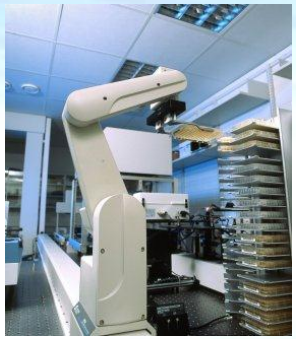
9. Experimental assays confirm toxicity



ELN

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

Synergy

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

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Sustainability Model

New Opportunity

K Base

K

K

Apps

Contract

Risk Assessments

Outcomes

Predictive Toxicology Collaboration Pool

Predictive Toxicology Virtual Organization

R&D Program Services & Support

Contract Payments

PRE-CREATION

CREATION

OPERATION

TERMINATION

Service Support of Virtual Organisation Lifecycle

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Our Drivers – Taking on Technical, Cultural and "Other" Challenges of the Unexpected

Visit with Lions at Mukuni Reintroduction Project, Livingstone, Zambia

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Final words...

For more information, visit

www.opentox.org

Contact me:

barry.hardy@douglasconnect.com

Many thanks for your attention!

OpenTox - An Open Source Predictive Toxicology Framework, www.opentox.org, is funded under the EU 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).

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SEVENTH FRAMEWORK PROGRAMME