Integrating Predictive Toxicology Model Development

SMi ADMET Conference

7,8 July 2010

Barry Hardy (Douglas Connect)

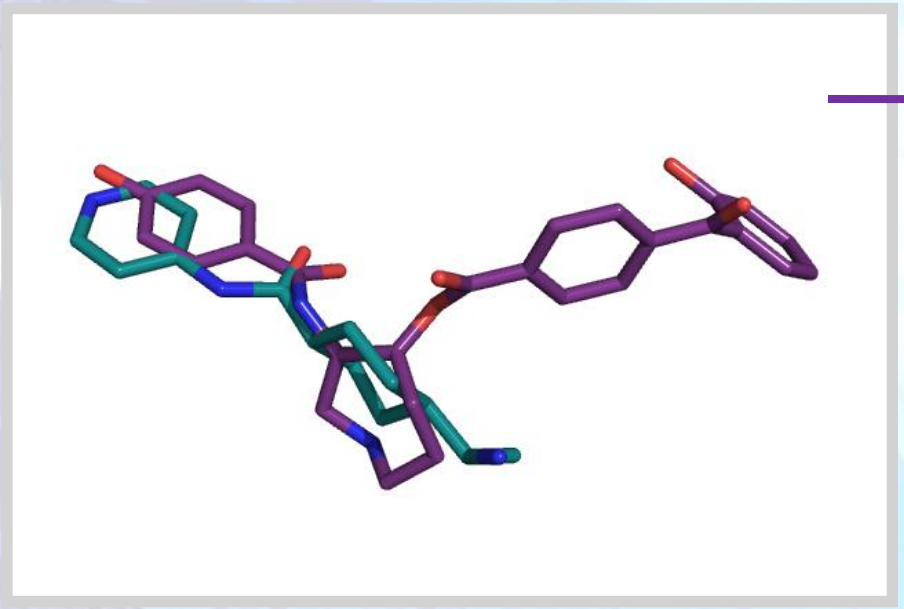
London, UK

OpenTox

SEVENTH FRAMEWORK PROGRAMME

Collaborative Predictive Toxicology Challenge

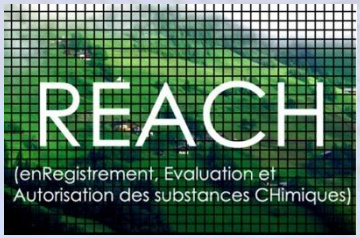
Input Structure



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 142k cmpds registered).

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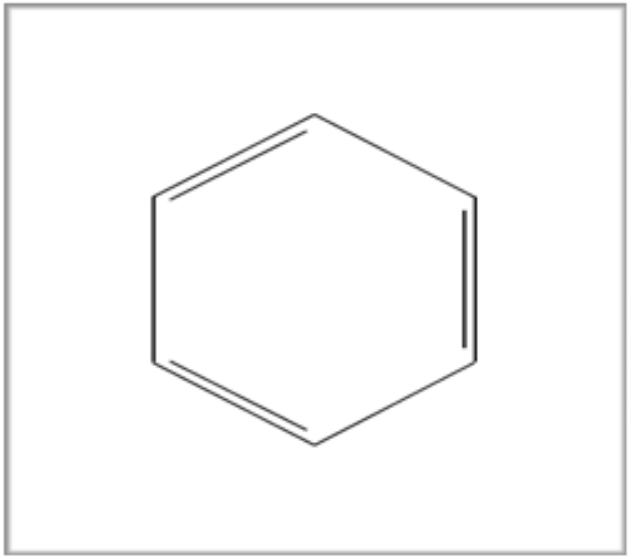
ToxPredict

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

Development of Strategies for Interoperable Resources & Applications in Predictive Toxicology

Eliminate
traditional circus acts, animals

CIRQUE DU SOLEIL

Create
theatrical themes, storylines, new acts

Blue Ocean

Reduce
dangerous acts, traditional humour, transport costs

Raise
tent standards, artistic sophistication, ticket prices!

Based on Blue Ocean Strategy, Kim & Mauborne 2006

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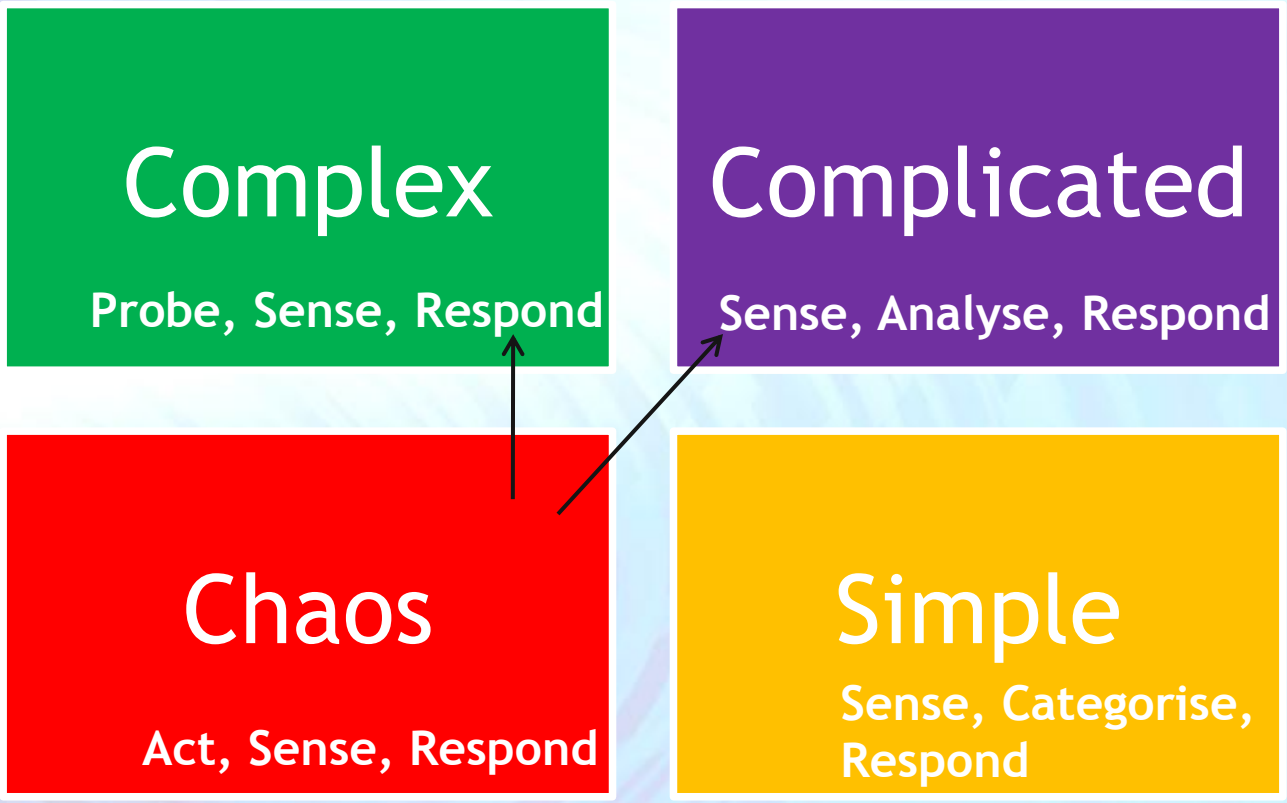
Based on Nonaka & Takeuchi, The Knowledge Creating Company, 1995

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

REACH

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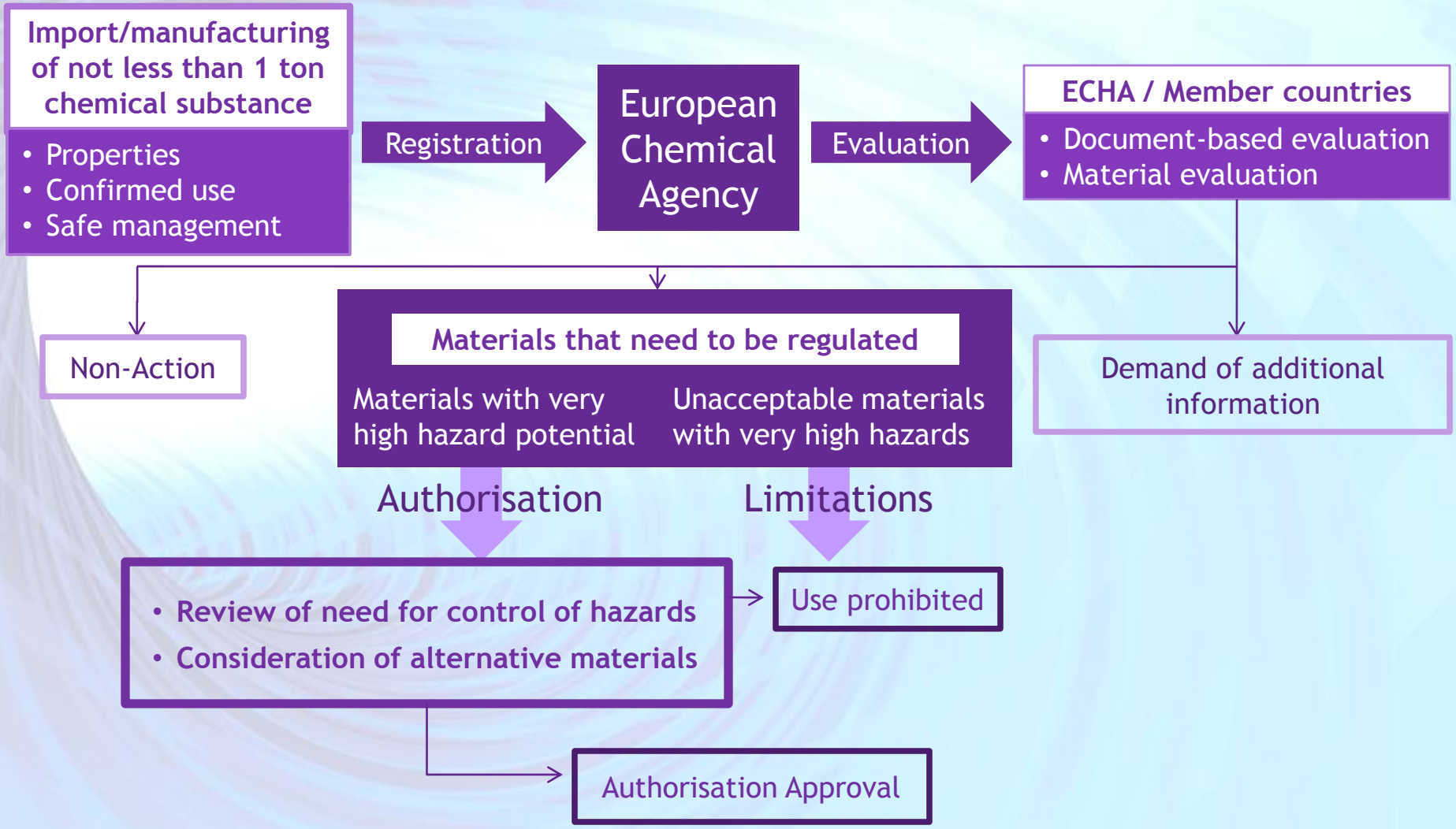
REACH Registration



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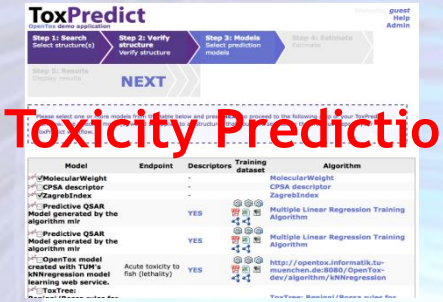
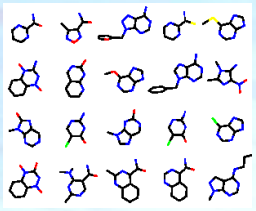
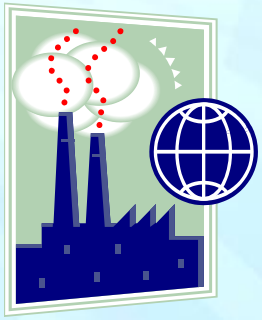
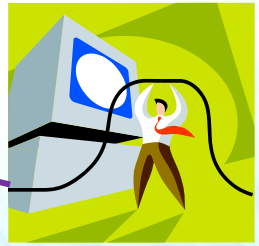
Accelerating Knowledge Flows in Predictive Toxicology

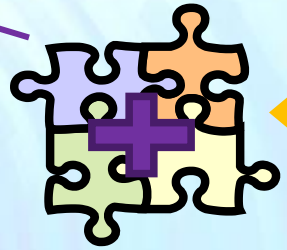


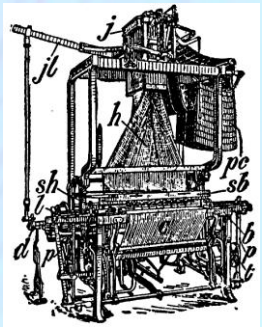
Toxicity Predictions











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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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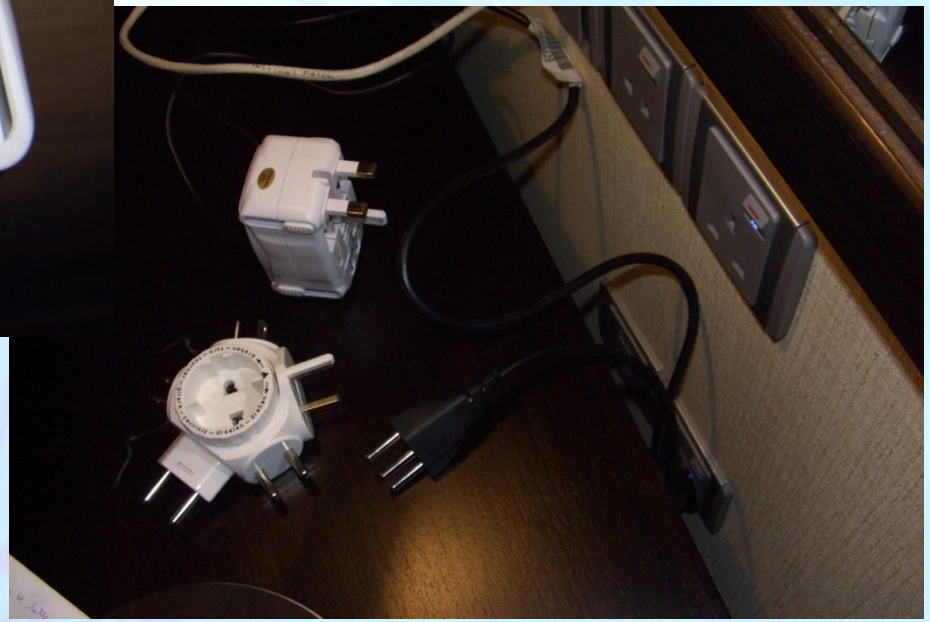
Absence of Interoperability creates Problems



Adaptor Challenge in Jeddah, 2008

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Interacting Components create Solutions

Adaptor Solution in Jeddah, 2008

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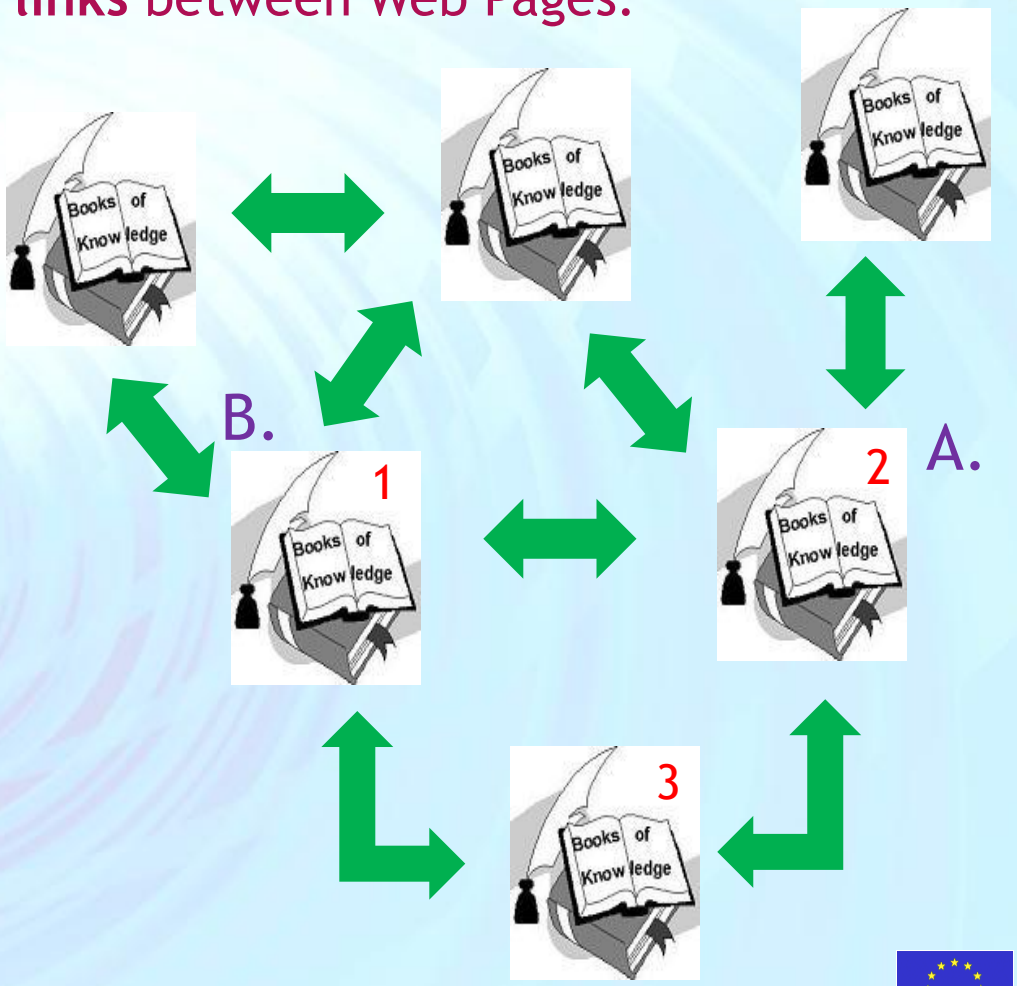
Value is in Linking

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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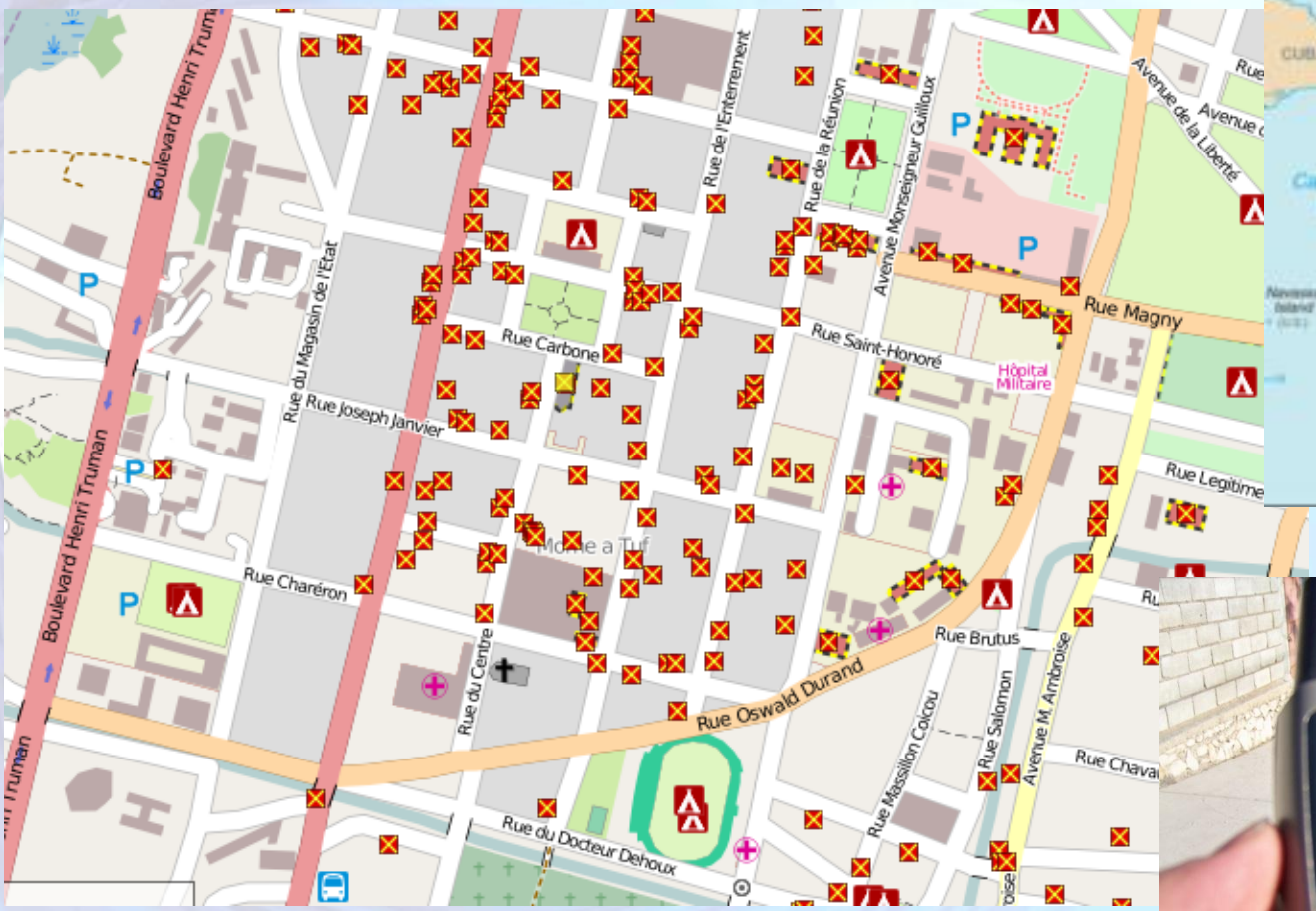
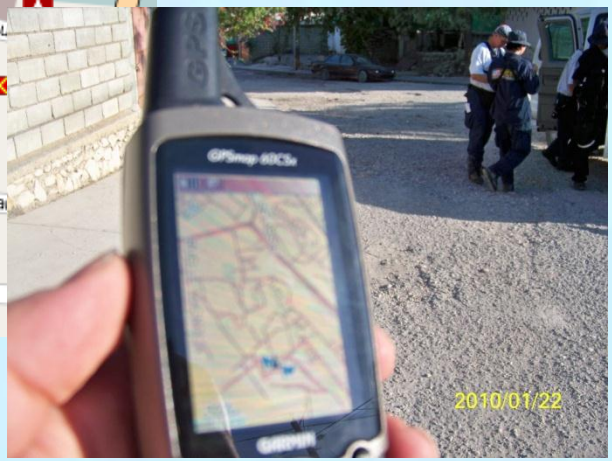
Solution created by Linked Open Data, Web Applications and Crowdsourcing





Haiti Earthquake Crisis Response (2010)

wiki.openstreetmap.org

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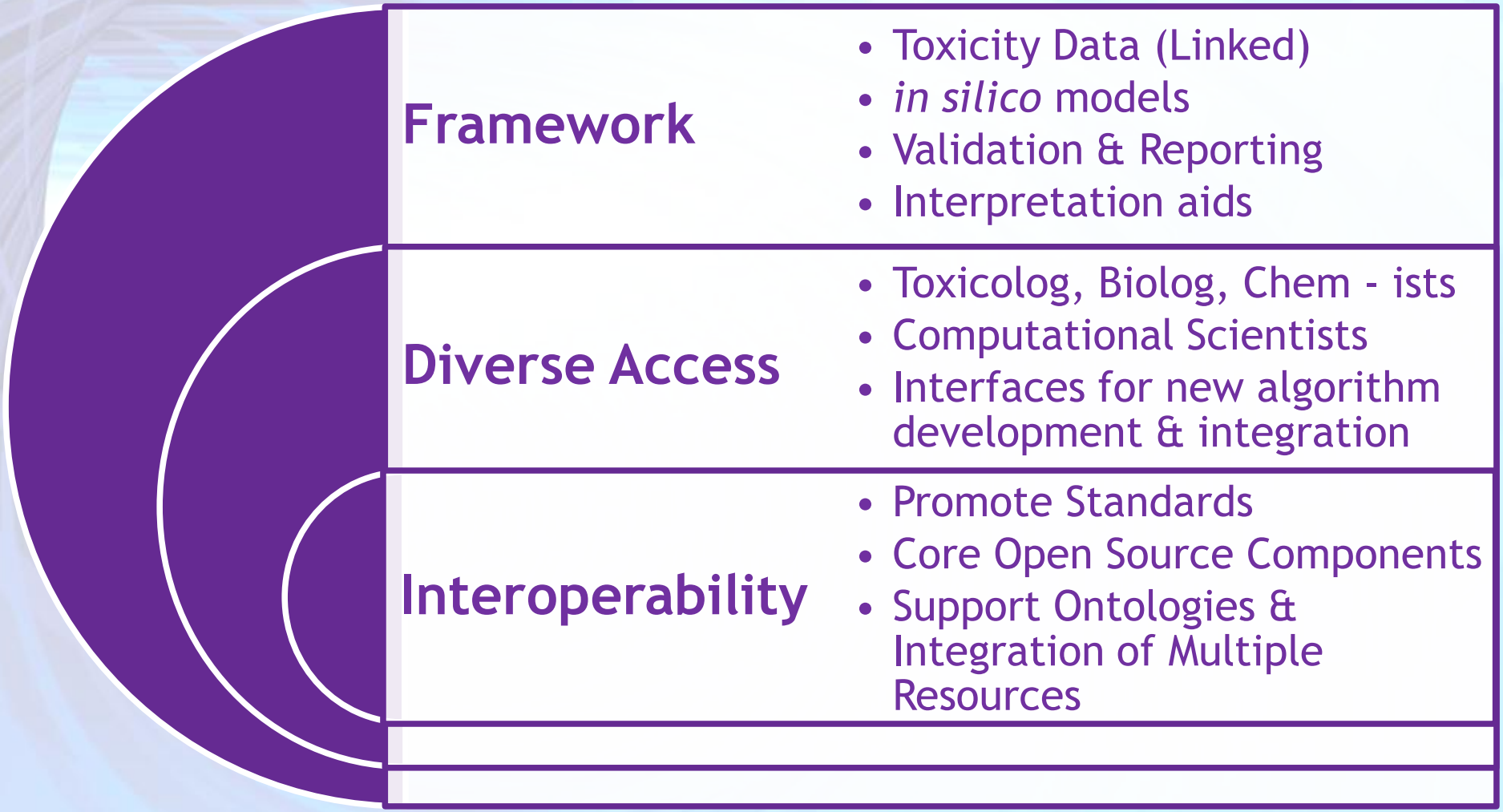
OpenTox is an Integrating Framework



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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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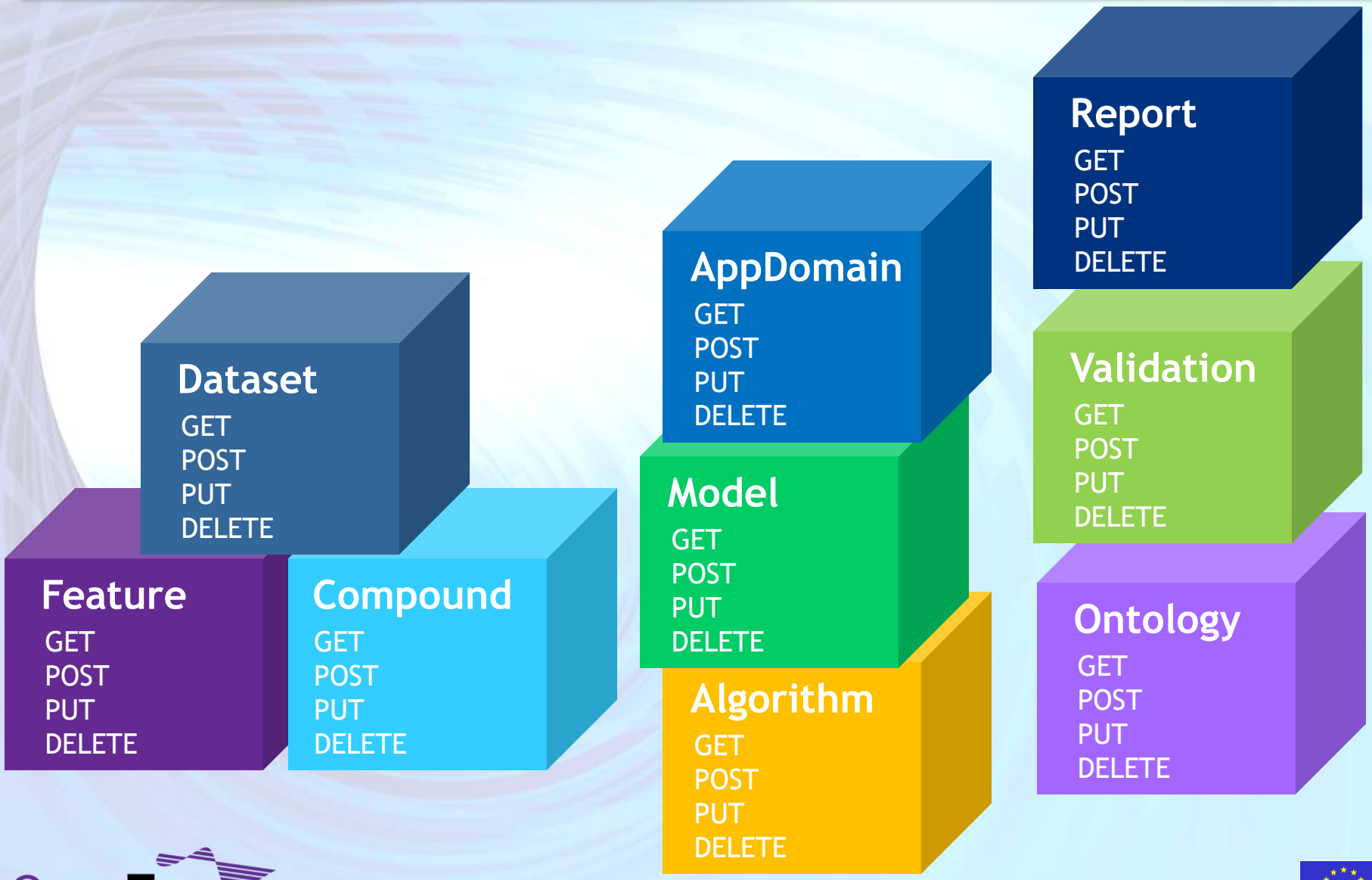
Overview of Application Programming Interfaces



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Representational State Transfer (REST): What and Why?

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 systems**
- (More or less) language independent/installation-free

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OpenTox Interface Definition Example

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

www.opentox.org/dev/apis

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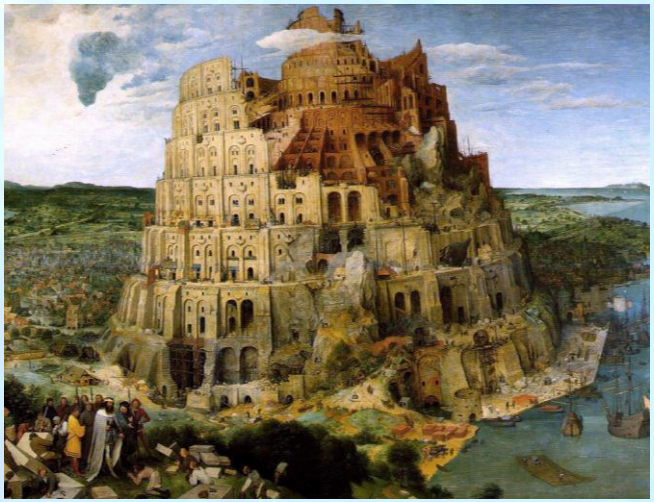
Ontologies: What and Why?

What?

- **Formal**, **shared conceptualization** of a **domain**

Why?

- Distributed services **need** to be able to "talk to each other", i.e. have a **common understanding** of endpoints, any type of property, methods, etc.



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Ontologies

- Standards: **OWL** as representation language and **SPARQL** as query language
- There are many ongoing biological ontology projects
- Our strategy: use existing work and standards wherever possible
- However, there are new ontology needs for OpenTox applications, e.g. for algorithms, toxicological endpoints

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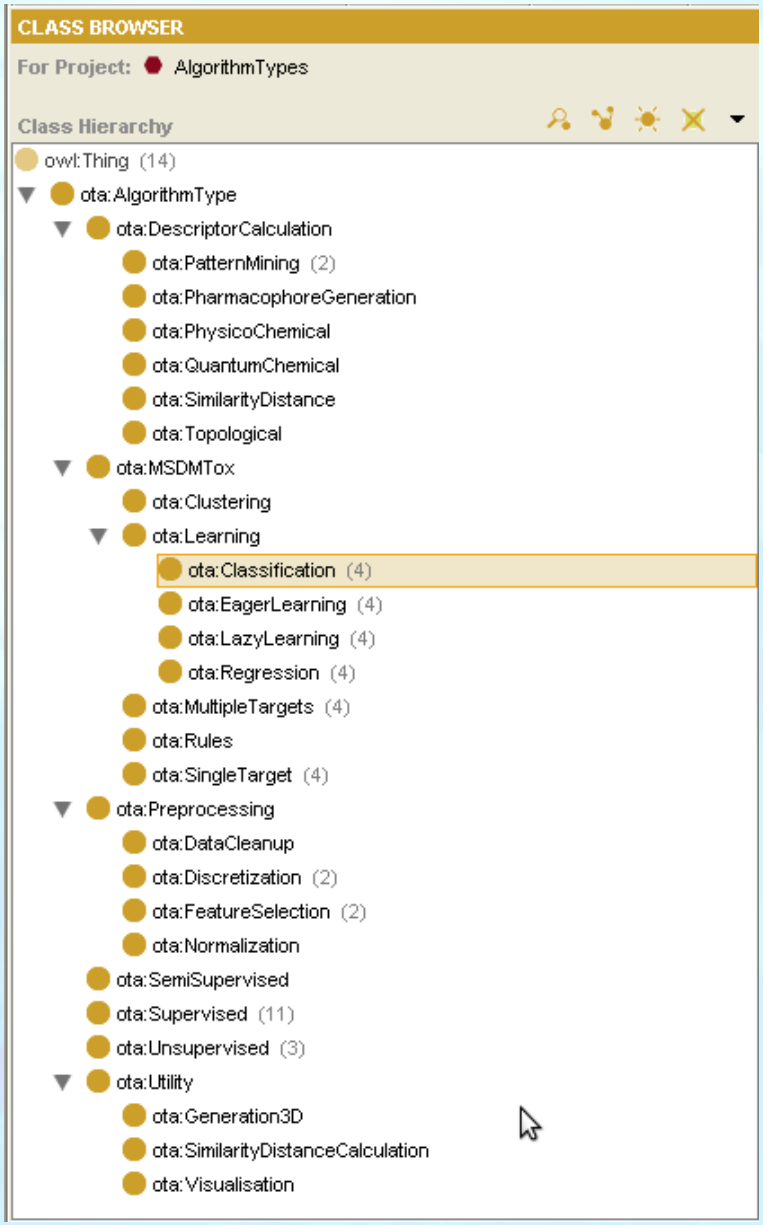
Ontology Working Group



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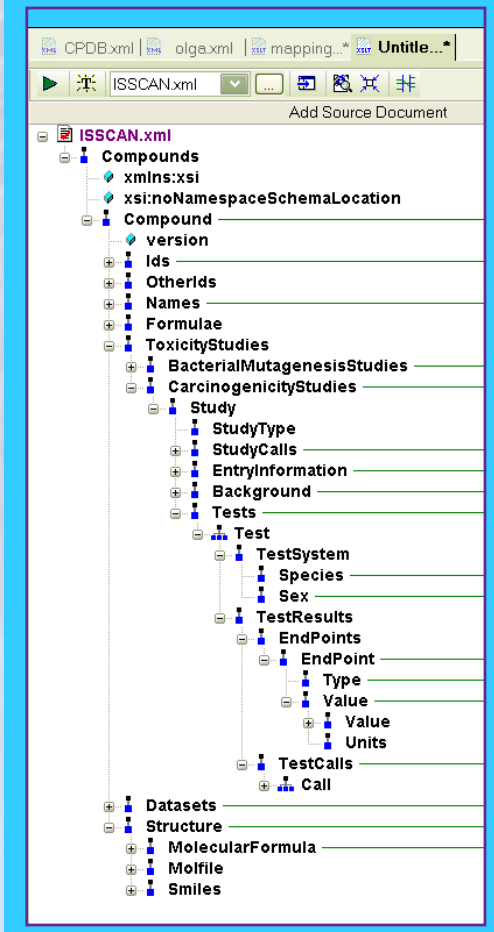
Toxicological Endpoint Ontology Development

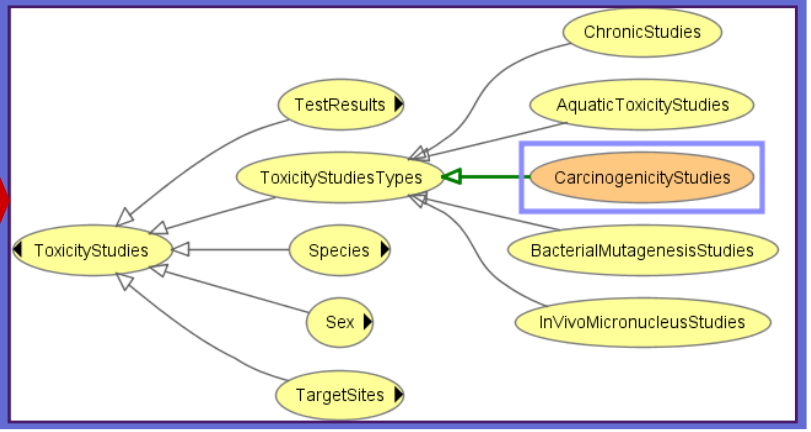
ToxML schema



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)

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OpenToxipedia

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OpenToxipedia

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

OpenTox Community Resource for Toxicology Vocabulary and Ontology

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

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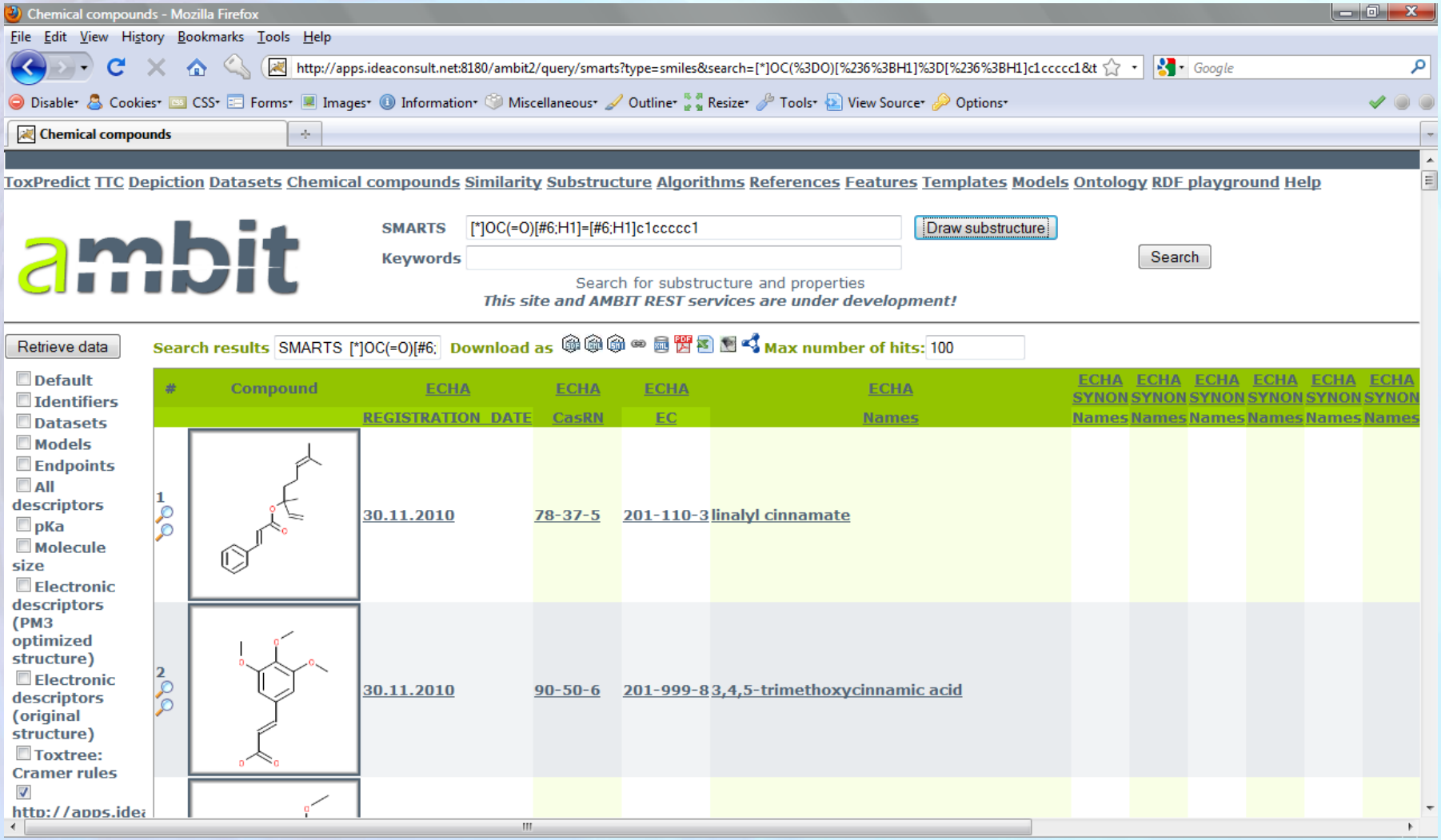
OpenTox: Databases



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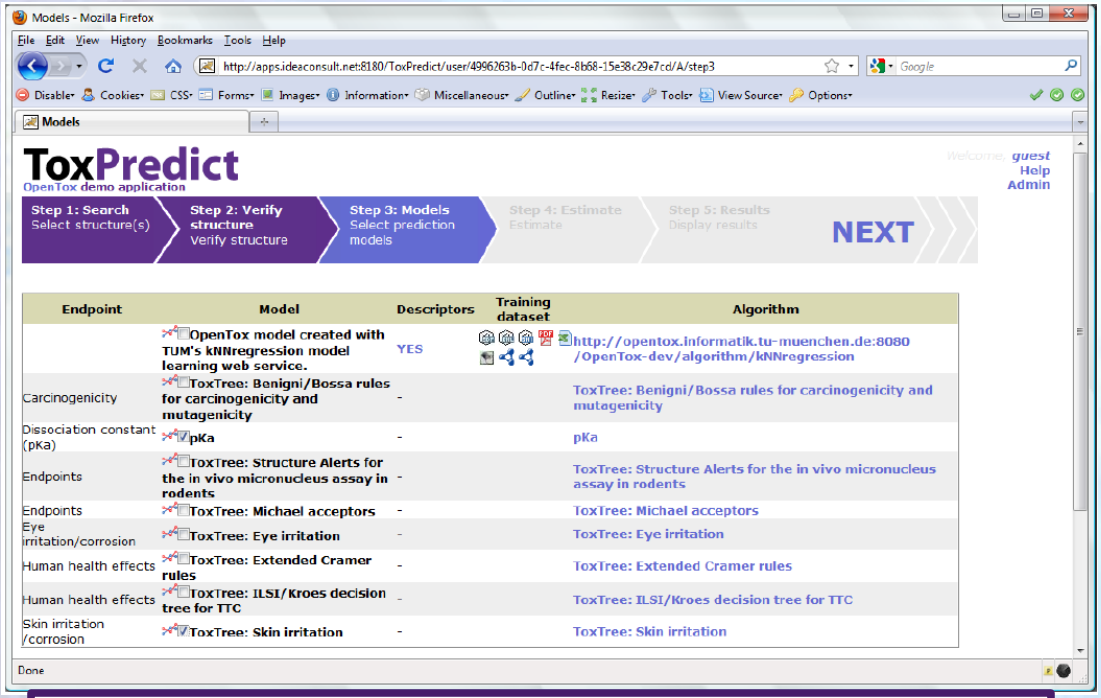
What you can do with it …



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

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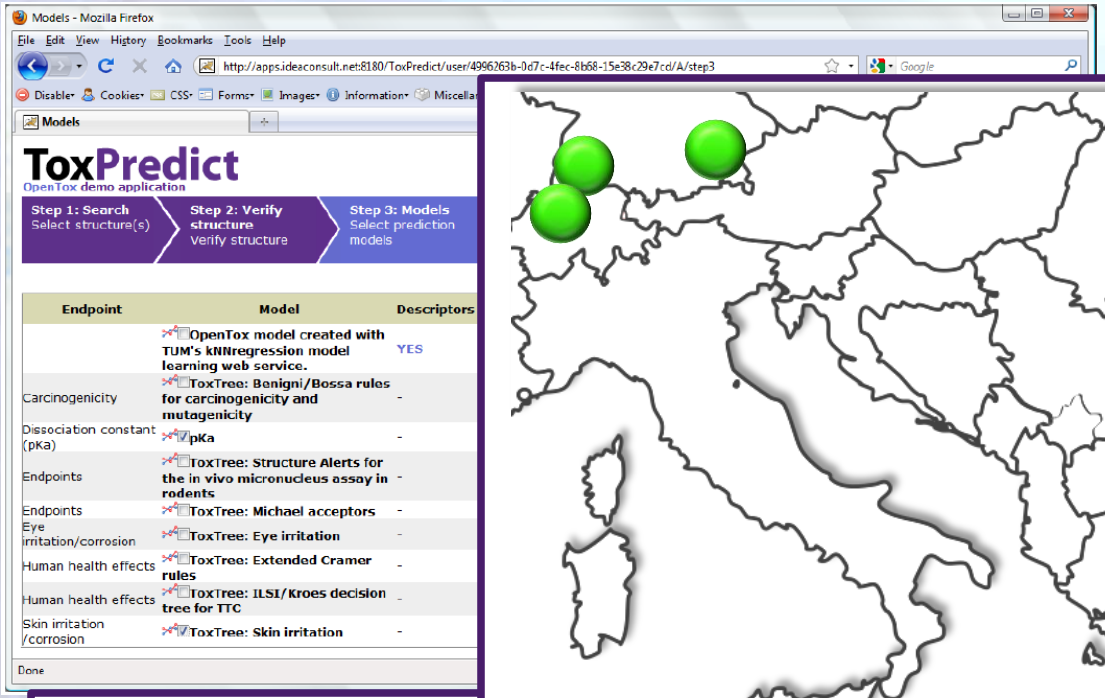
What you can do with it …



Simple building c

applications

methods and

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

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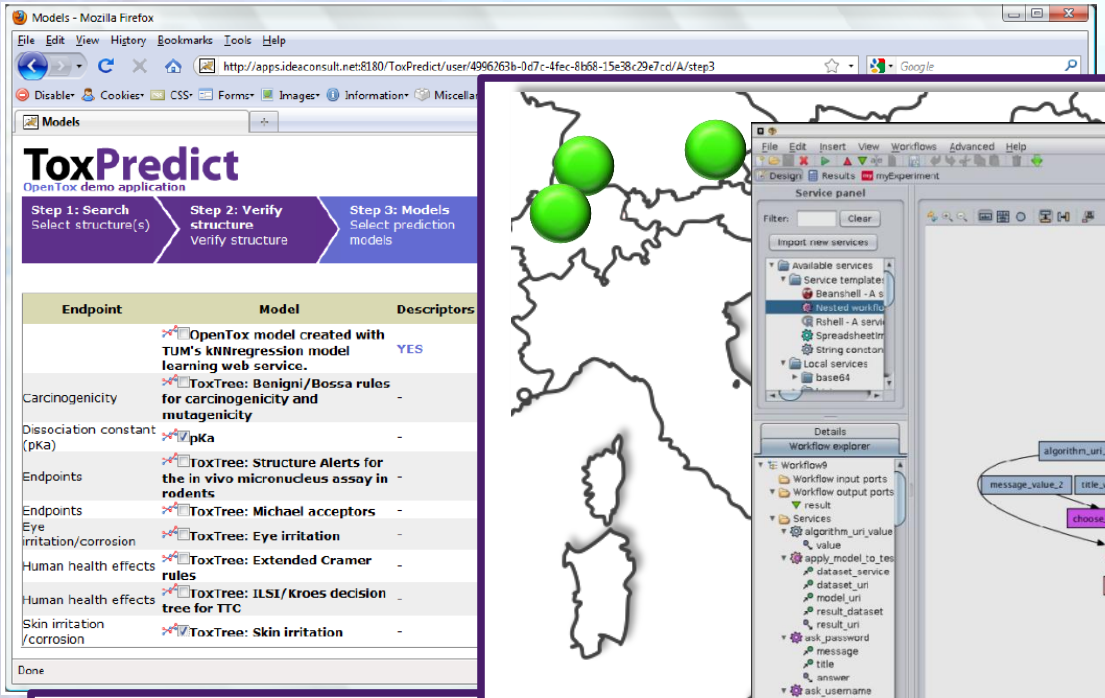
What you can do with it …



Simple building applications methods and

Distributed wide range methods

Integration into workflow systems for computational biology

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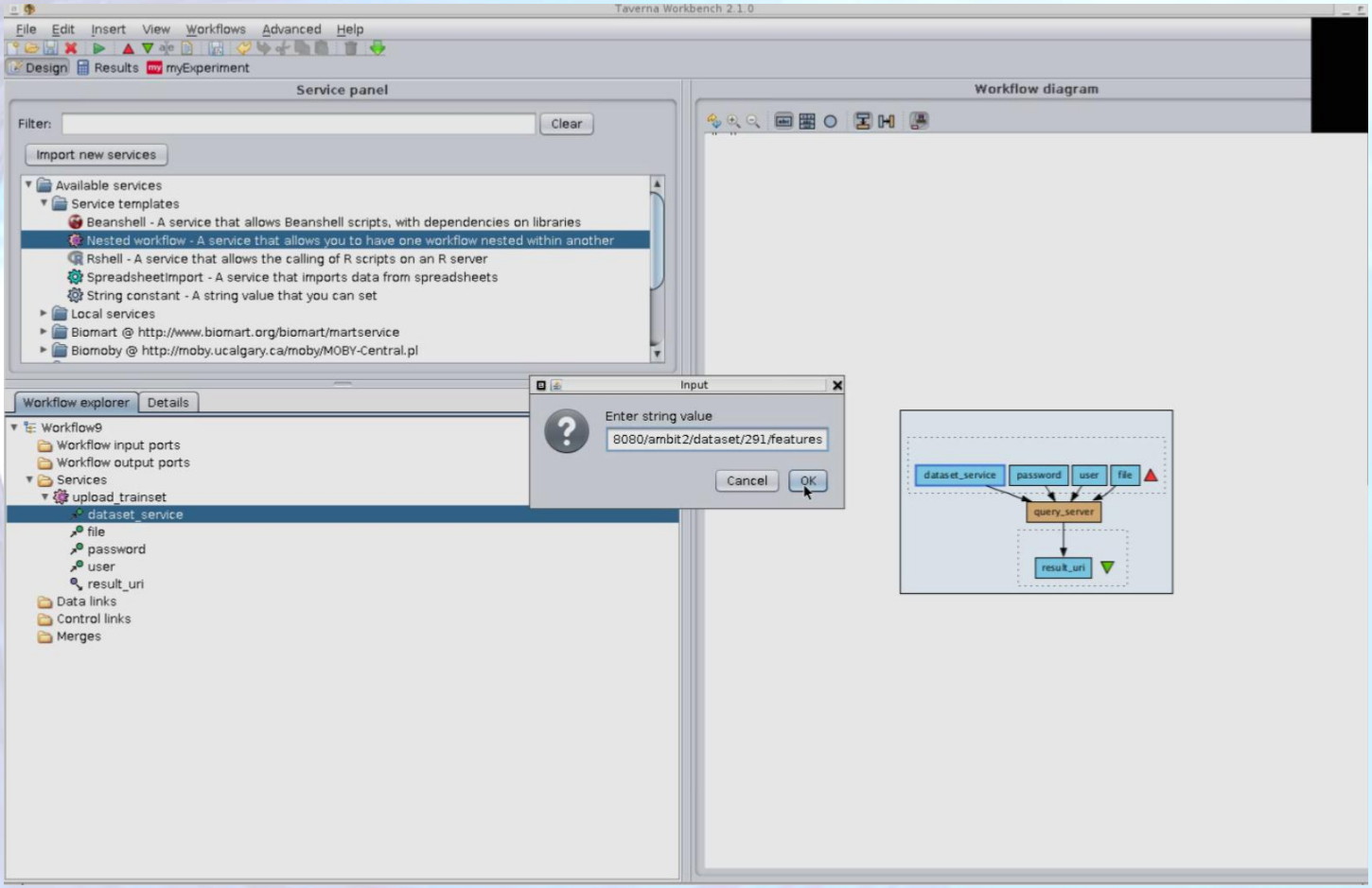
Workflows Connecting OpenTox services

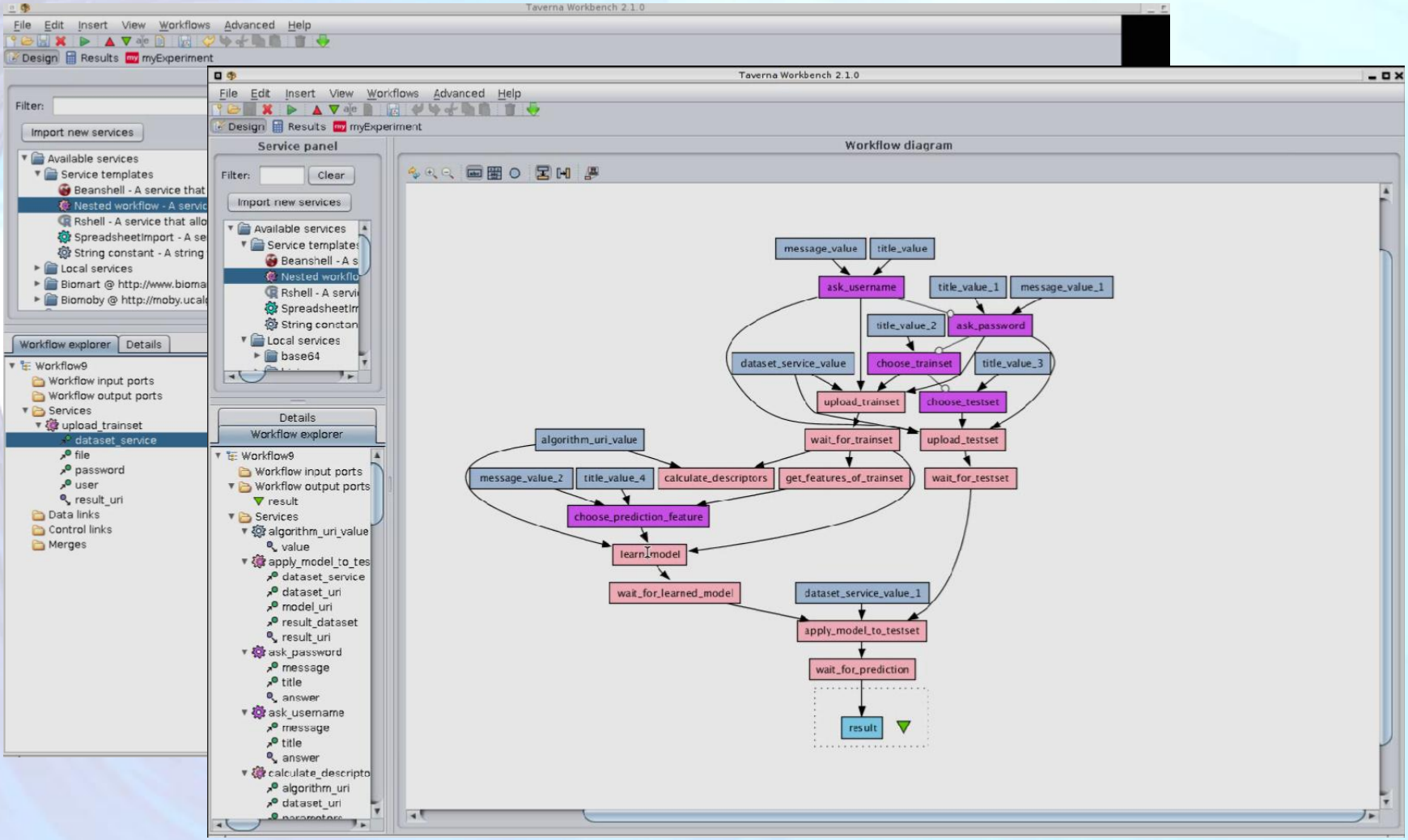
- OpenTox services can be integrated into workflows of tasks using workflow systems such as Taverna
- Supports the execution of multiple services in both synchronous and asynchronous tasks
- Goal is to support the integration of distributed chemical and biological data and modelling resources in more complex applications

Taverna Workflow System & OpenTox Services



Test workflows are provided for download under MyExperiment

Taverna Workflow System & OpenTox Services



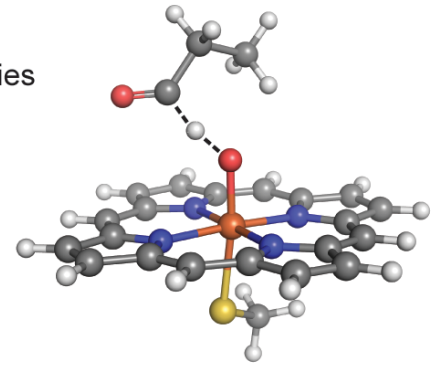
Test workflows are provided for download under MyExperiment

SMARTCyp Service for Predicting Metabolites

Atom Reactivity Library

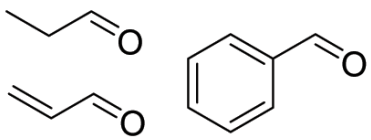
A. Calculate Quantum Chemical Reference Energies

Calculate transition state energies using density functional theory



B. Define SMARTS Rules

Group calculations by fragments and calculate average energies



[CX3H1](=O)[#6]

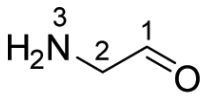
40.2 kJ/mol

SMARTCyp - developed by Patrik Rydberg, University of Copenhagen

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

SMARTCyp

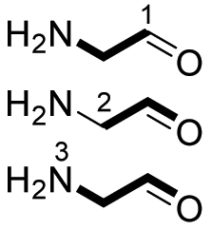
1. Assign Energies By SMARTS matching



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

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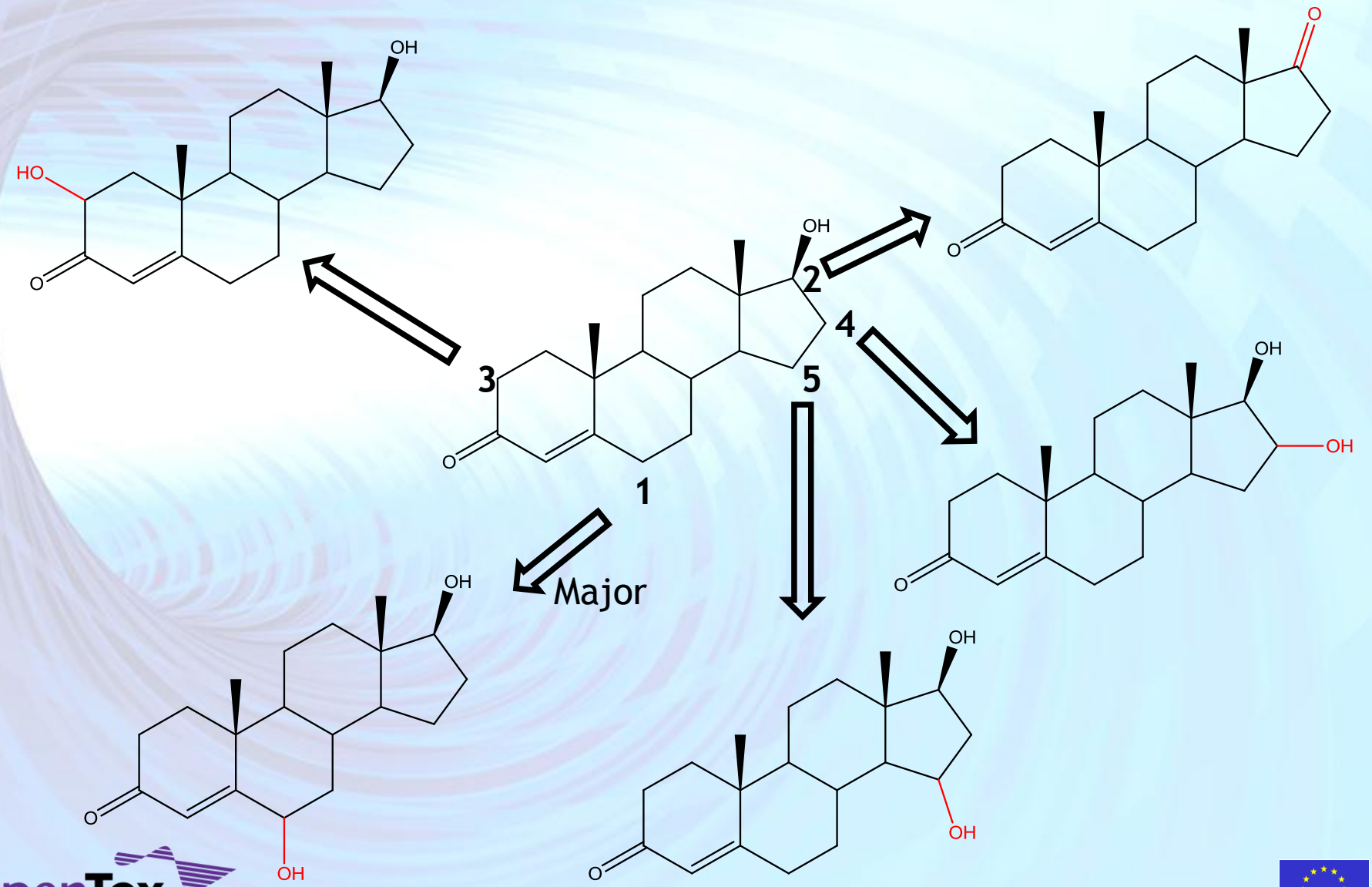
SmartCYP Prediction of Testosterone Metabolites



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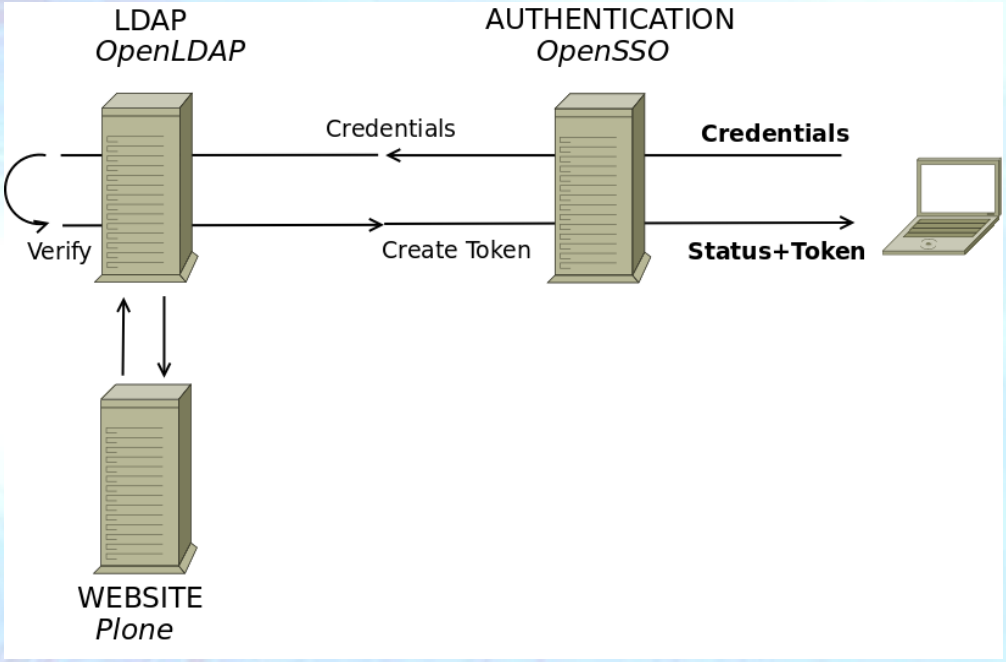
Controlling Access to Confidential Information

- 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

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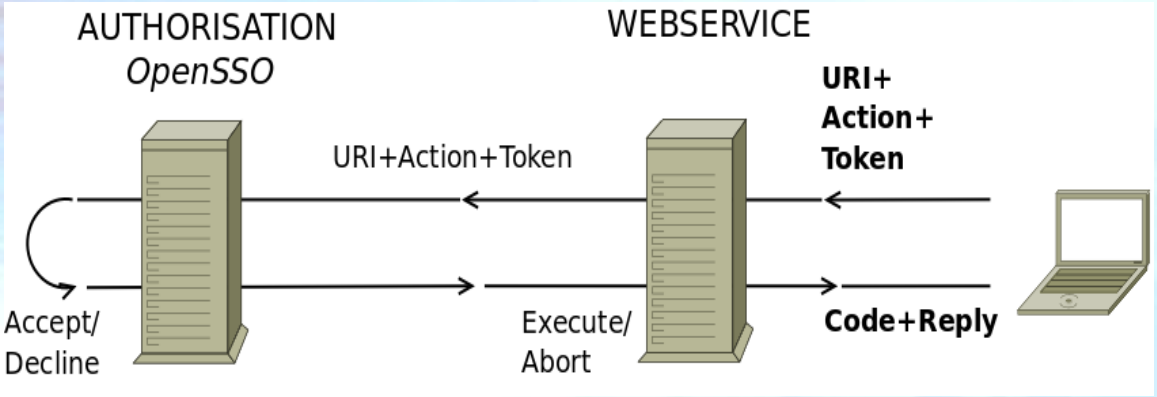
Authorisation



- 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

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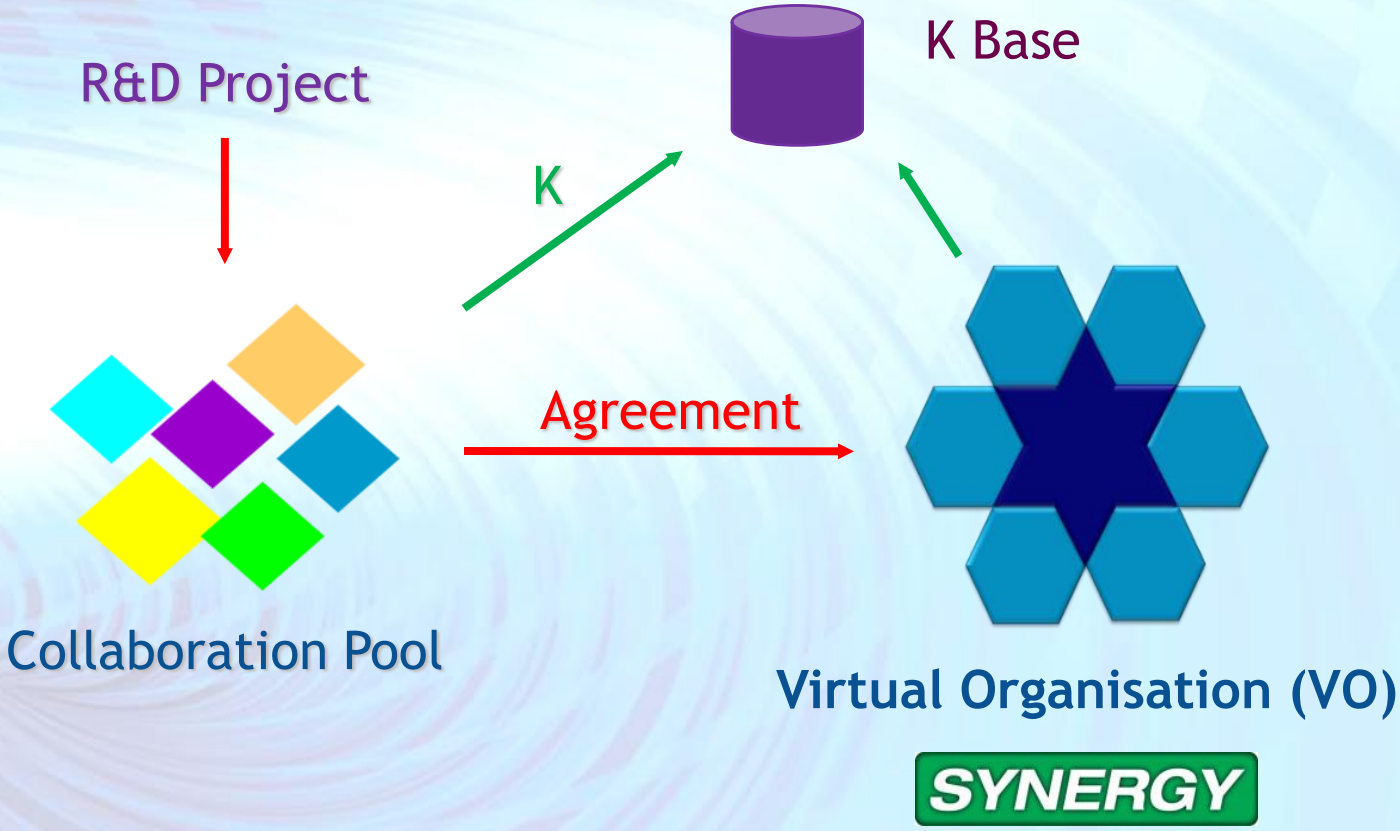
Virtual Organisation Pilots



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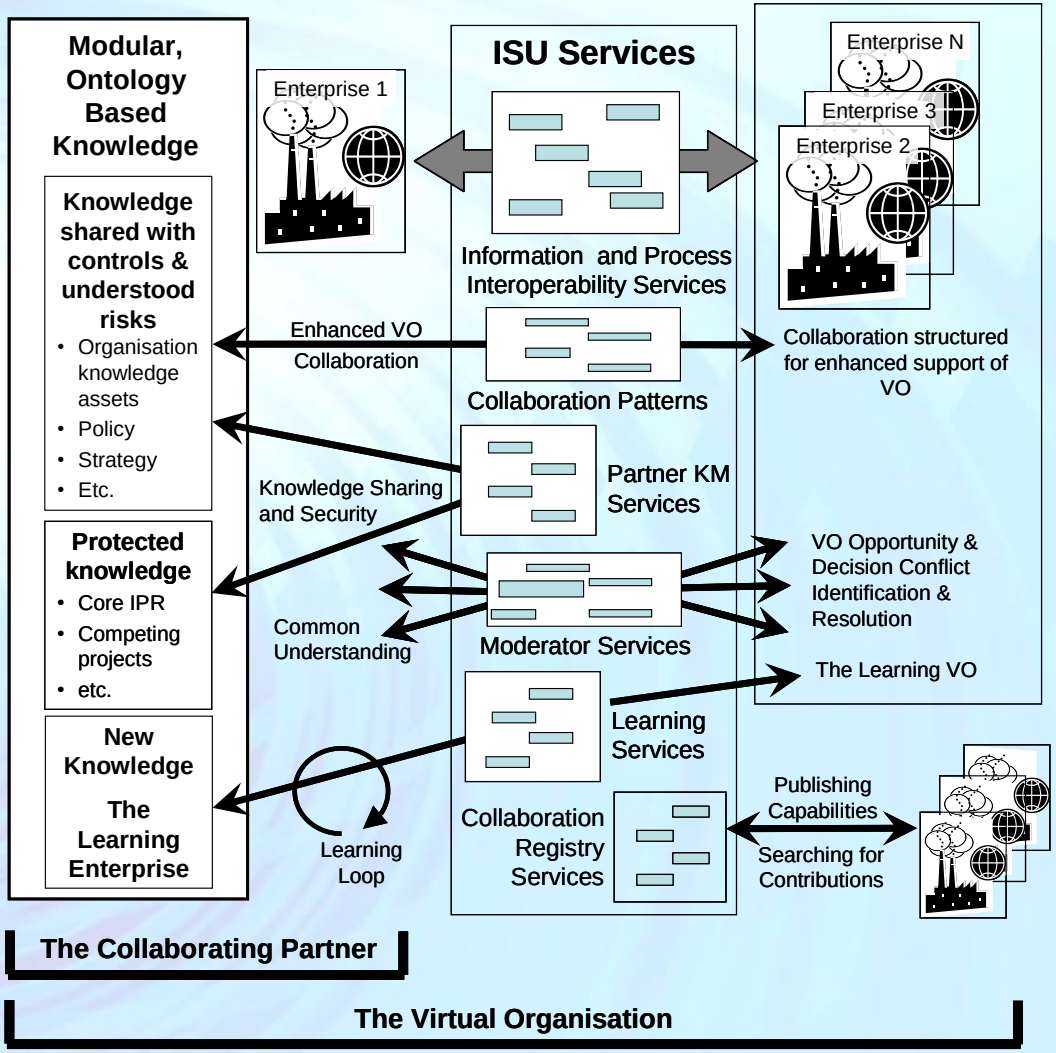
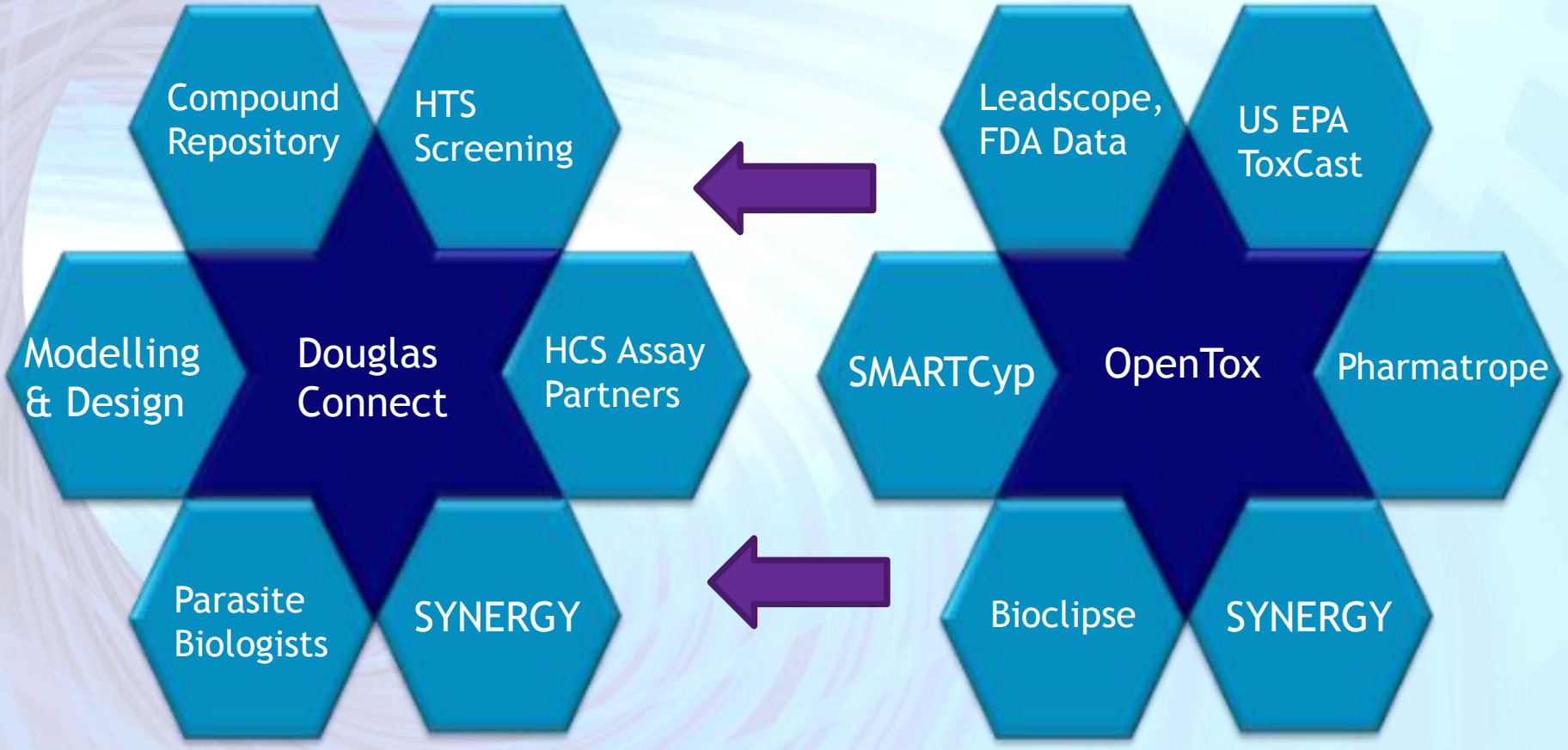
SYNERGY Collaboration Services for VOs

SYNERGY website:
www.synergy-ist.eu/



Virtual Organisation Pilots



Neglected Disease Drug Design VO

Predictive Toxicology VO

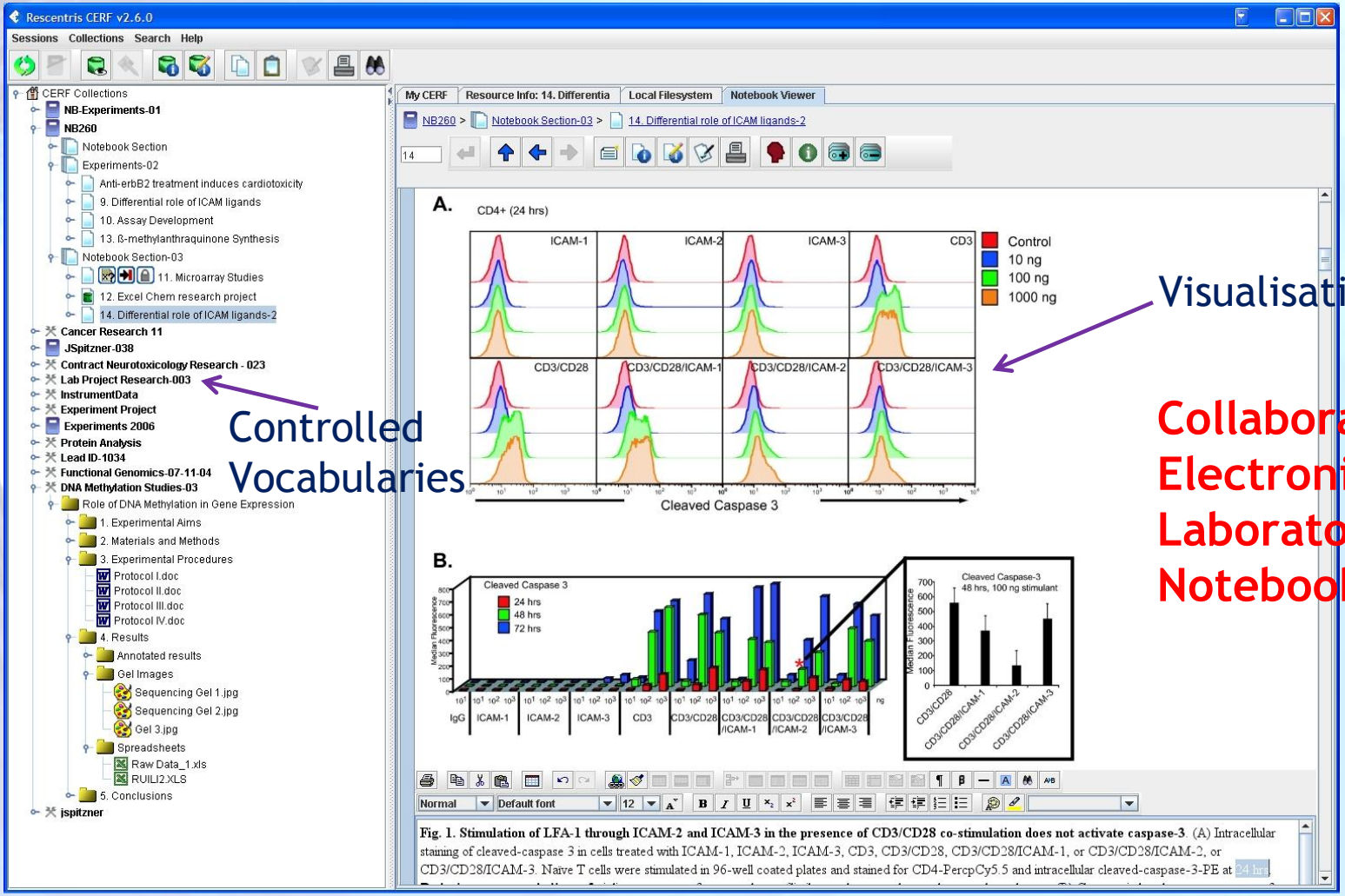
OpenTox

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

Recording of Collaborative R&D



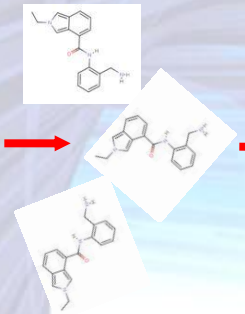
Controlled Vocabularies

Visualisation

Collaborative Electronic Laboratory Notebook (ELN)

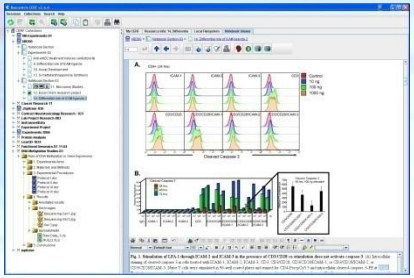
OpenTox

Synergy Collaboration Pilots

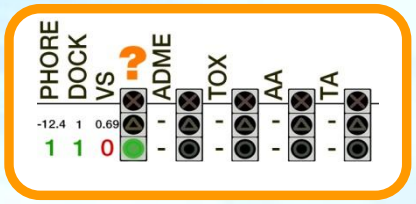


Screened Library

Data

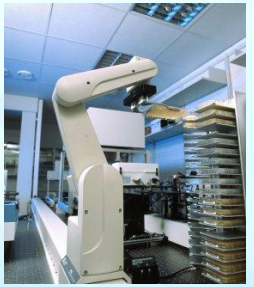


CERF

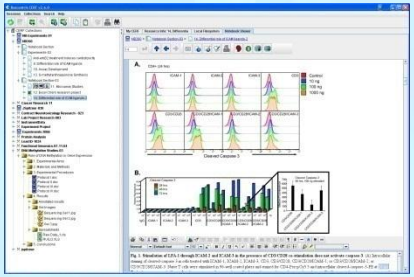


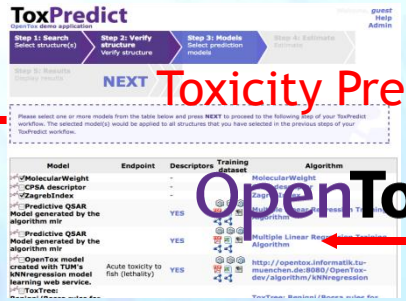
Refine Predictions

SYNERGY



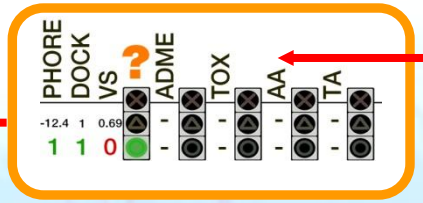
Data



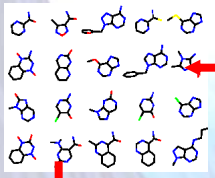


Toxicity Predictions

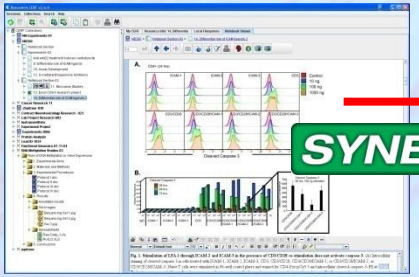
OpenTox



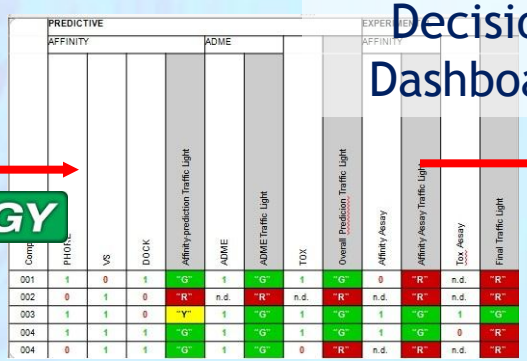
SYNERGY



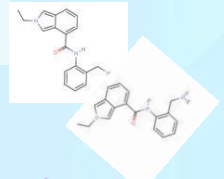
Toxicity Assays



SYNERGY



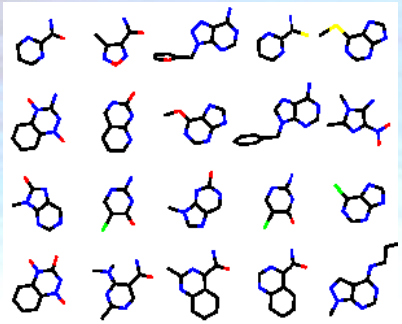
Decision Dashboard



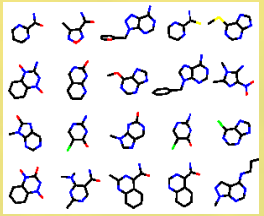
(Safer) Drug Leads

OpenTox

1. A library of compounds is entered to the ELN



ELN

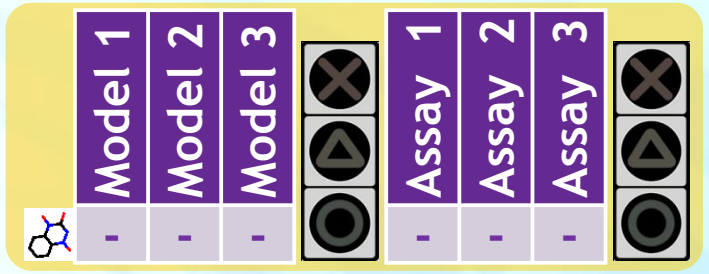


Synergy

OpenTox

2. Each compound is assigned a data structure in ELN

ELN

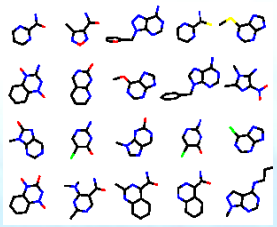


Synergy

OpenTox

OpenTox

3. ELN passes compounds to OpenTox and SYNERGY



ELN

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

Synergy

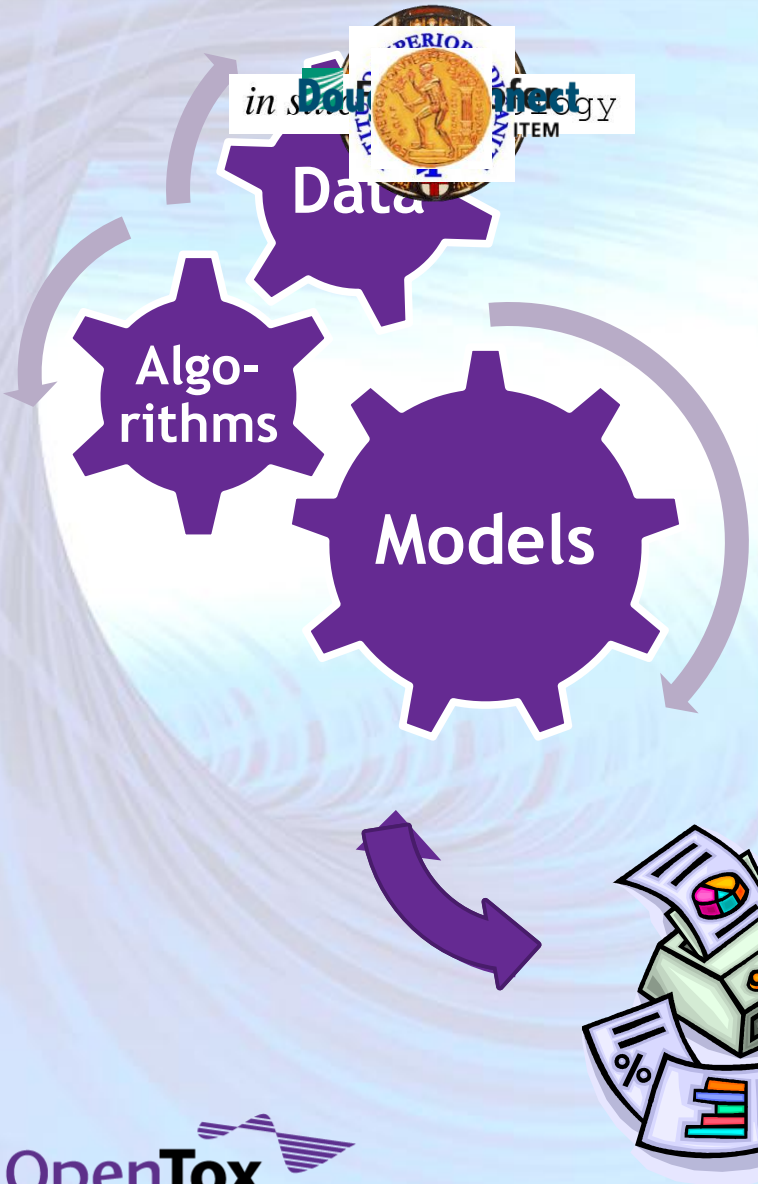
	Model 1	Model 2	Model 3		Assay 1	Assay 2	Assay 3	
	-	-	-		-	-	-	

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

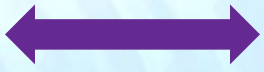
Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
1	0	1	-	-	-

OpenTox

6. ELN sends the results to SYNERGY

OpenTox

7. SYNERGY applies the Recommendation Rules



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	-	-	-

OpenTox

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	-	-	-

OpenTox

OpenTox

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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Acknowledgements - OpenTox Partners

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Alexey Lagunin
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Indira Ghosh
Surajit Ray
Gaurav Singhai
Om Prakash
Sylvia Escher
Sara Weiss
Helvi Grimm

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- Leadscope
- University of North Carolina
- EC Environment Directorate General
- Organisation for Economic Cooperation & Development
- CADASTER
- Bayer Healthcare

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Final words...

For more information, visit

www.opentox.org

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Many thanks for your attention!

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SEVENTH FRAMEWORK PROGRAMME