Satisfying REACH Requirements in Predictive Toxicology

Accomplishments & Challenges in Global Chemicals Policy

22 July, 2010

IUTOX, Barcelona, Spain

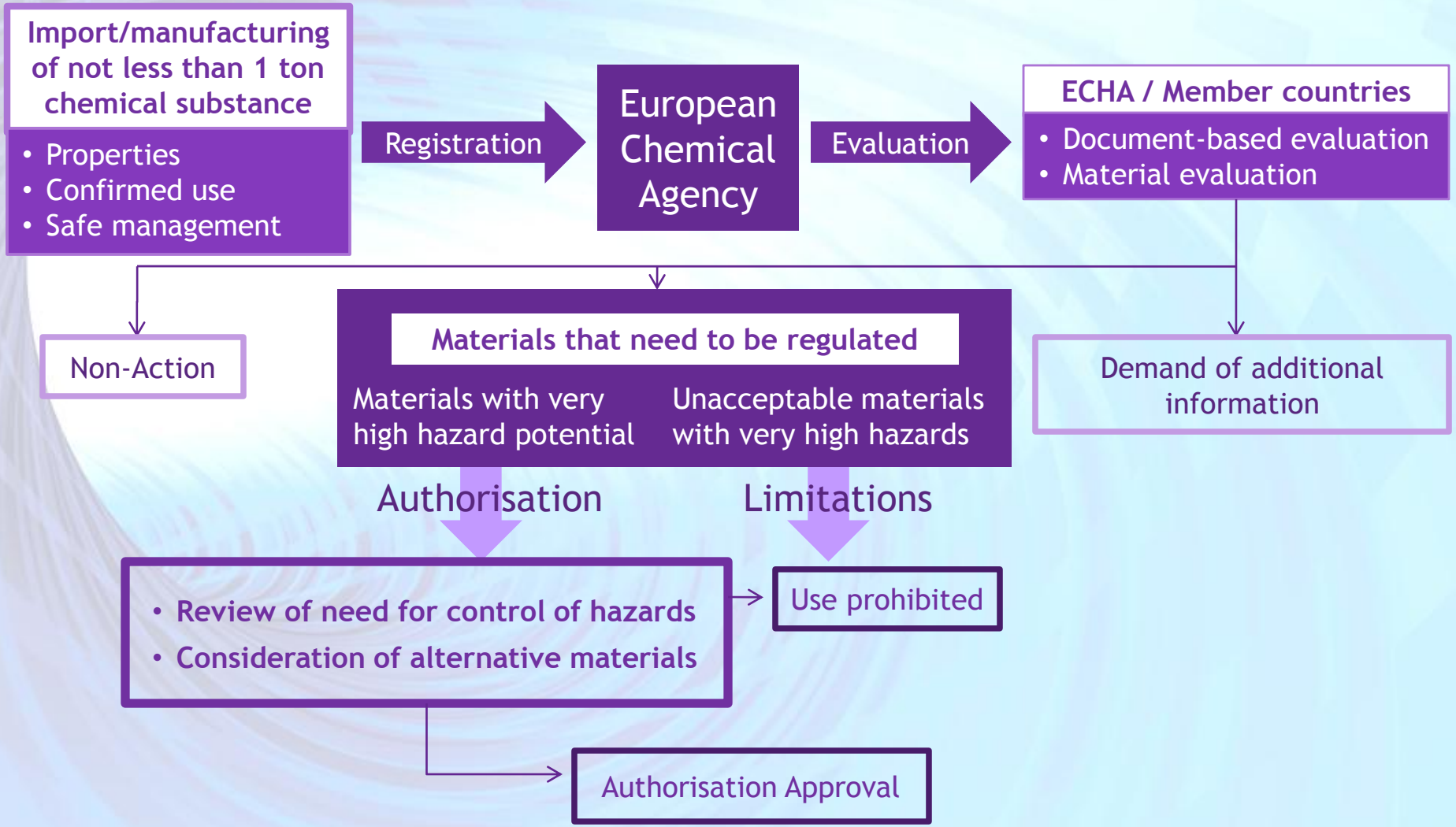
OpenTox

SEVENTH FRAMEWORK PROGRAMME

REACH

OpenTox

REACH Registration, Evaluation & Authorisation



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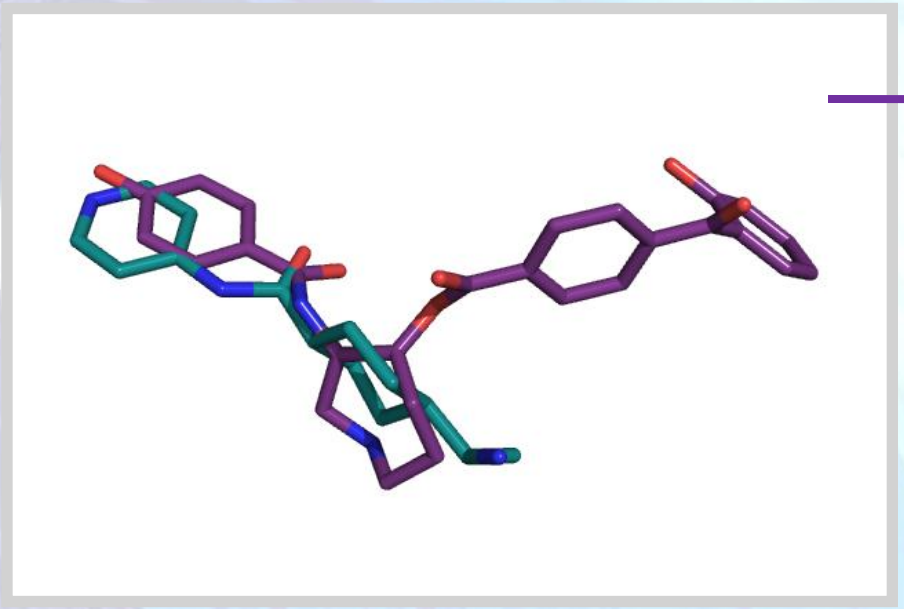
Collaborative Predictive Toxicology Challenge

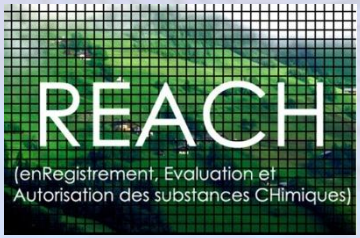
Input Structure



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.

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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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What is our situation today when we say ...

Let's build an integrated predictive toxicology application!

Let's collaborate on an analysis!

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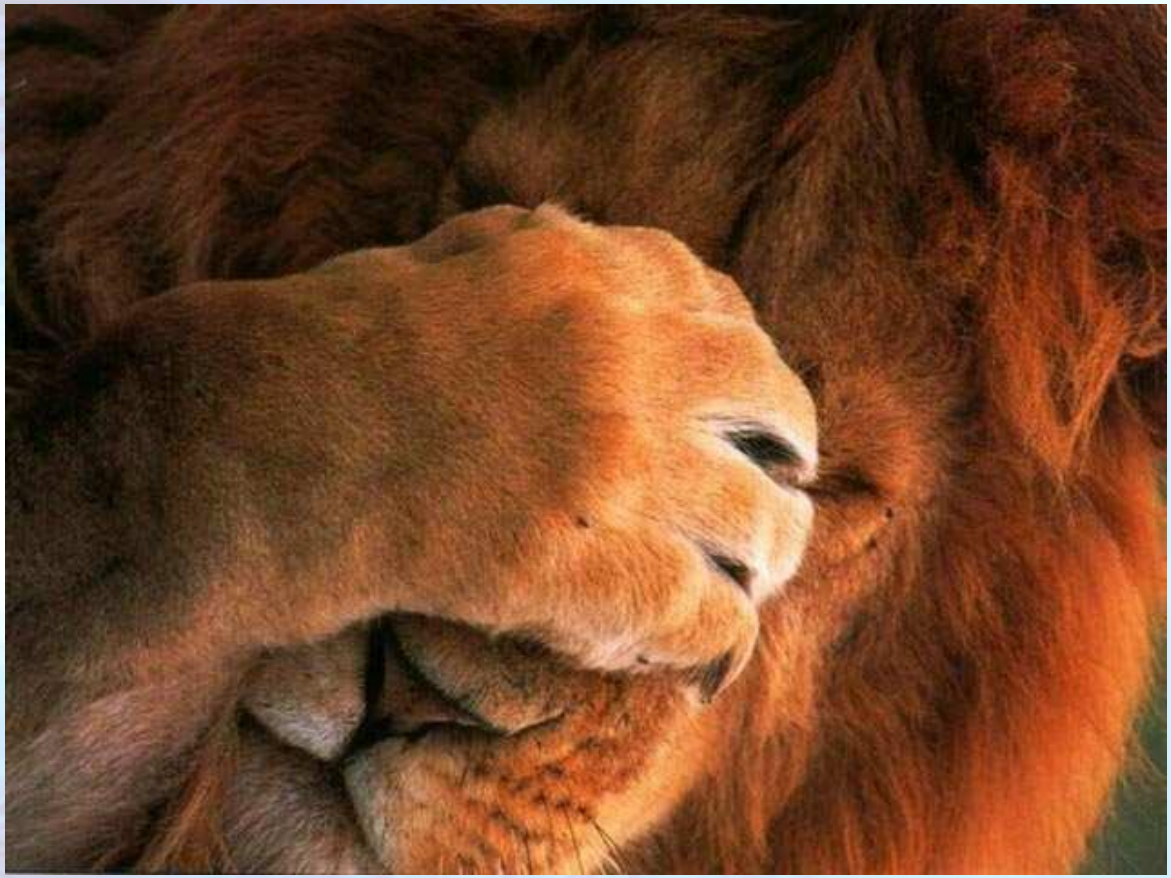
Faced with such an integration challenge ...



... we tend to look away from some of the problems ...

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Faced with such an integration challenge ...

... we tend to look away from some of the problems and from the need to collaborate more closely.

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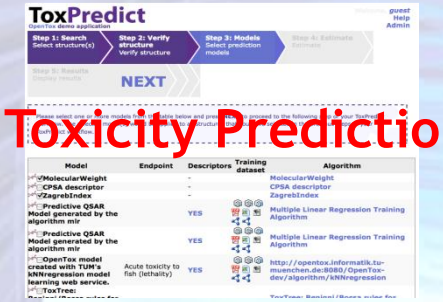
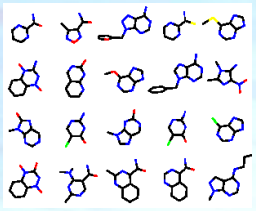
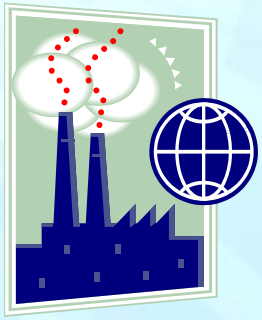
Based on Nonaka & Takeuchi, The Knowledge Creating Company, 1995

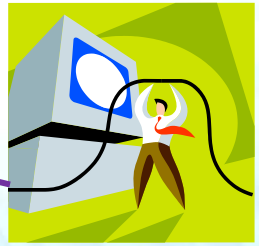
Accelerating Knowledge Flows in Predictive Toxicology

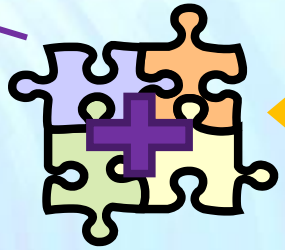


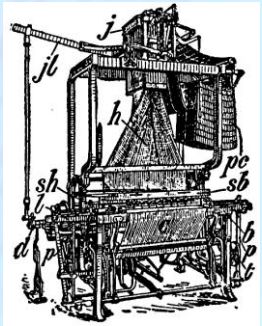
Toxicity Predictions











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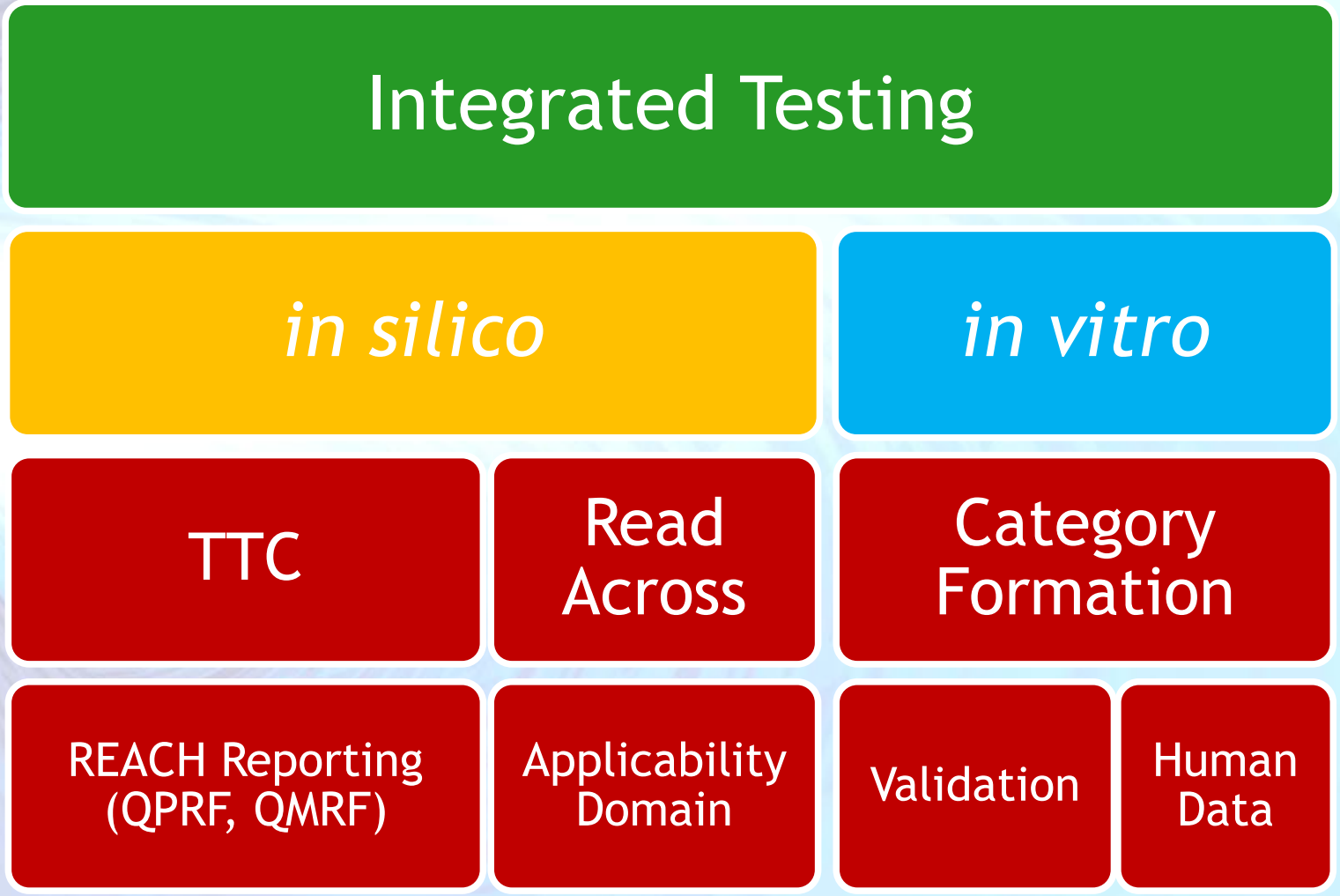
Compelling Needs of Users



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

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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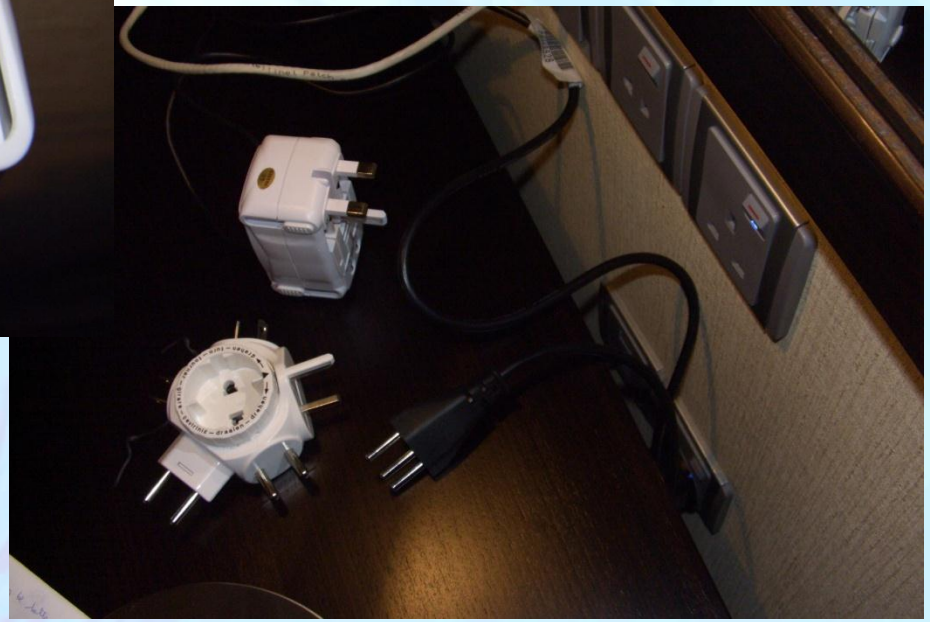
Absence of Interoperability creates Problems



Adaptor Challenge in Jeddah, 2008

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Interacting Components create Solutions

Adaptor Solution in Jeddah, 2008

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OpenTox Framework - Standards

Minimum Information Standards for Biological Experiments

en.wikipedia.org/wiki/Minimum_Information_Standards)

- Minimum Information for Biological and Biomedical Investigations (MIBBI) www.mibbi.org
- Functional Genomics Experiment (FuGE) fuge.sourceforge.net/
- MAGE www.mged.org/index.html,
- MIAPE www.psidev.info/index.php?q=node/91
- Predictive Model Markup Language (PMML) www.dmg.org/pmml-v3-0.html

Toxicity Data

- DSSTox www.epa.gov/ncct/dsstox/
- ToxML www.leadscope.com/toxml.php
- PubChem pubchem.ncbi.nlm.nih.gov/
- OECD Harmonised Templates www.oecd.org/document/13/0,3343,en_2649_34365_36206733_1_1_1_1,00.html
- IUCLID5 templates

  iuclid.eu/

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OpenTox Framework - Standards

Validation

Algorithm Validation

- common best practices such as k-fold cross validation, leave-one-out, scrambling

QSAR Validation (Model Validation)

- OECD Principles www.oecd.org/dataoecd/33/37/37849783.pdf
- QSAR Model Reporting Format (QMRF) qsardb.jrc.it/qmrf/help.html
- QSAR Prediction Reporting Format (QPRF) ecb.jrc.it/qsar/qsar-tools/qrf/QPRF_version_1.1.pdf

Reports

REACH

- Guidance on Information Requirements and Chemical Safety Assessment

Part F

- Chemicals Safety Report
- Appendix Part F guidance.echa.europa.eu/guidance_en.htm

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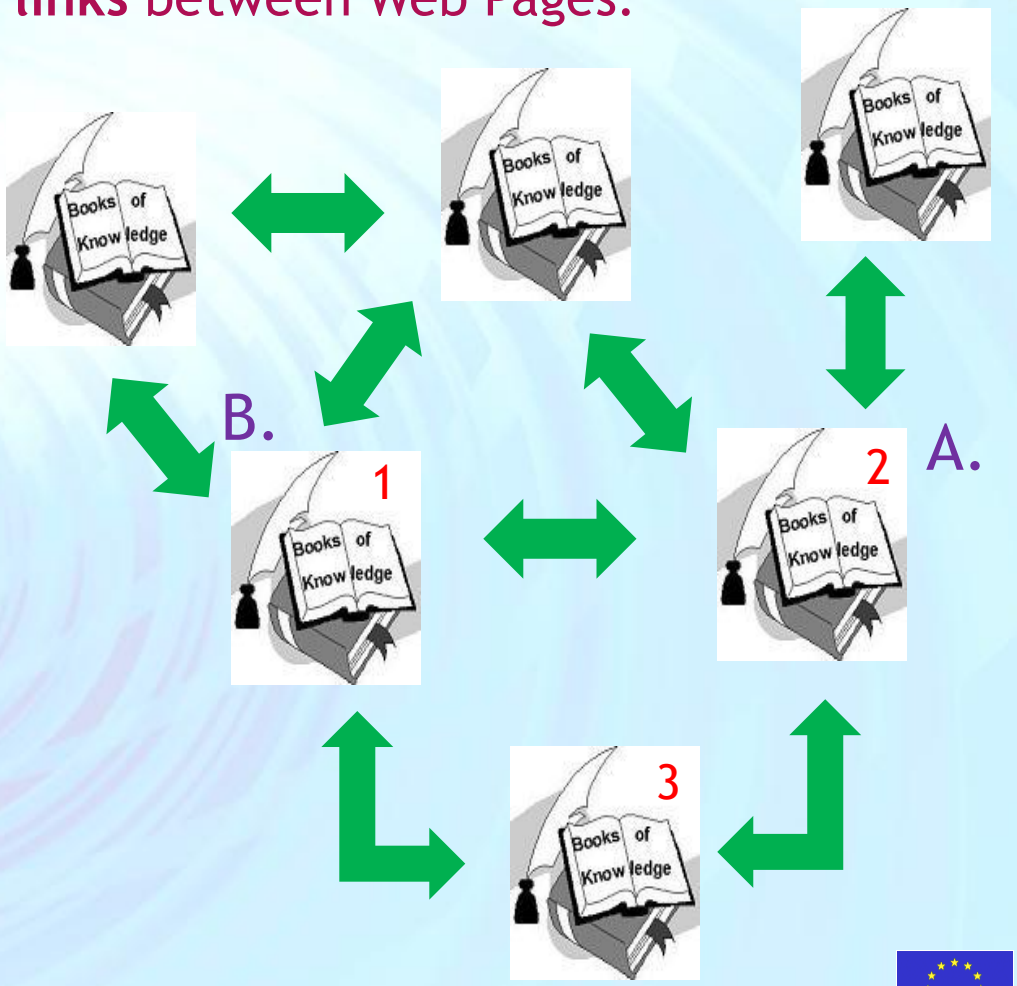
Value is in Linking

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:

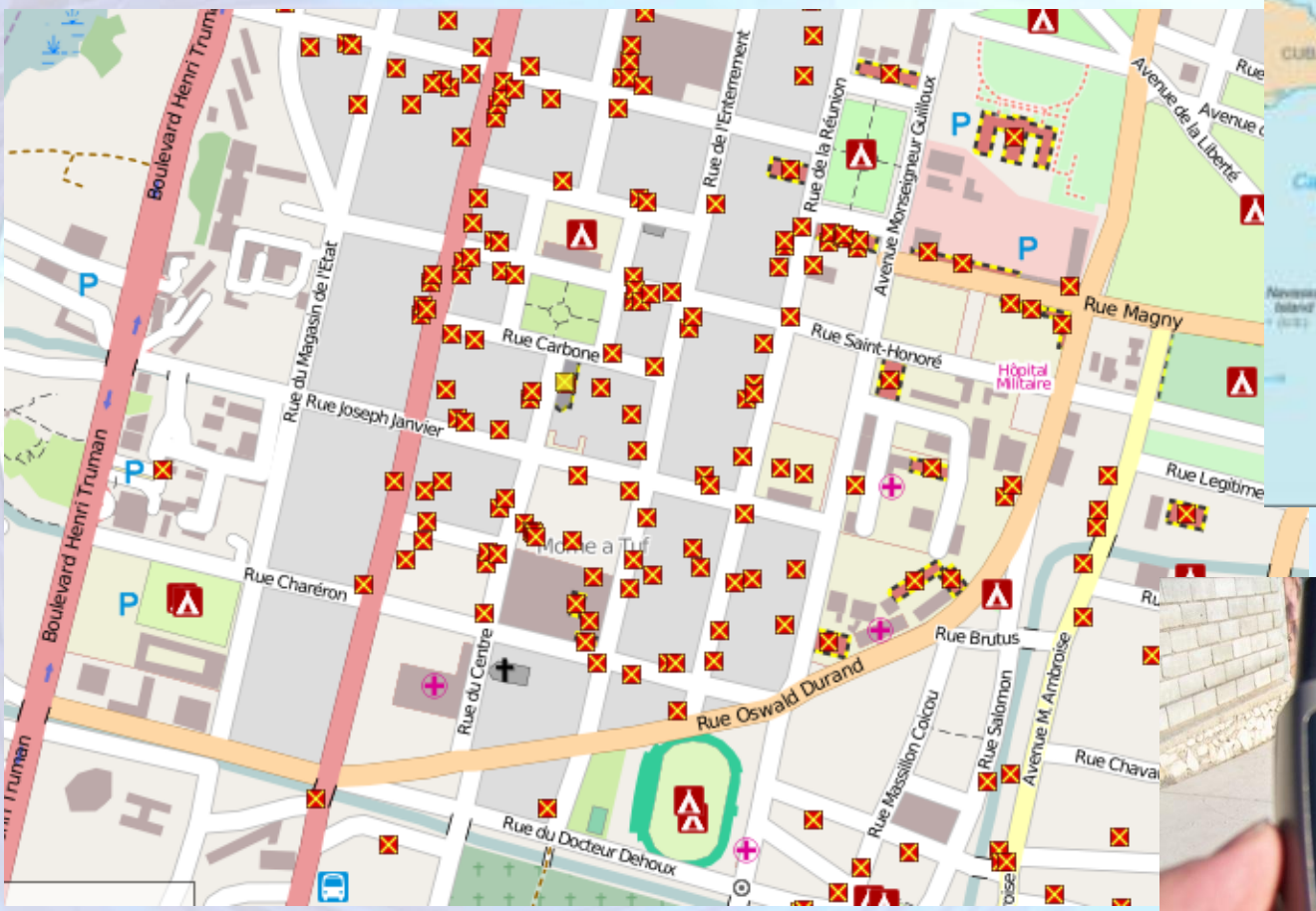
1. Provision of a **URI** that describes a Data Resource
2. Use of **HTTP** to retrieve useful data from the **URI**
3. A Data Format described with standardised semantics (so relationships are enabled) e.g. **RDF**
4. Data should provide links to other Data (through **URIs**)

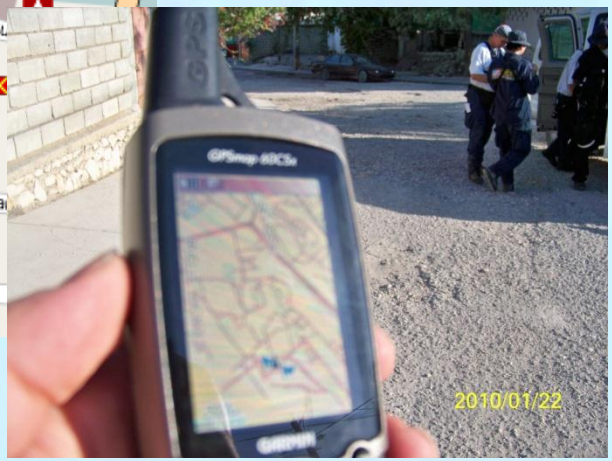
Linked Data approach can also be applied to other resource types e.g., for algorithms or models as done in OpenTox…

DBpedia = Linked Data approach applied to Wikipedia

OpenTox

Solution created by Linked Open Data, Web Applications and Crowdsourcing





Haiti Earthquake Crisis Response (2010)

wiki.openstreetmap.org

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Interoperability & Vocabulary

Dogs
- Collie
- Labrador

Cats
- Siamese
- Persian

Birds
- Sparrow
- Owl

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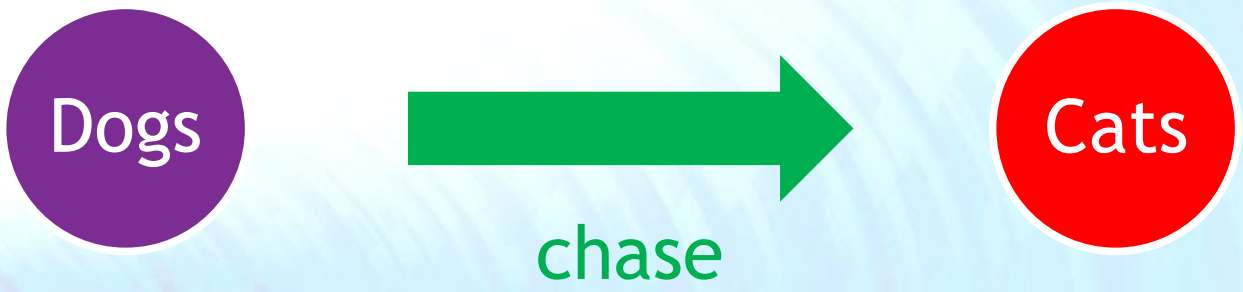
Interoperability & Vocabulary



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Interoperability & Ontology

Org A

Collie

chase

Siamese

Org B

Collie

Siamese

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	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 prediction of toxicological mechanisms and the recording of opinions and analysis in reports

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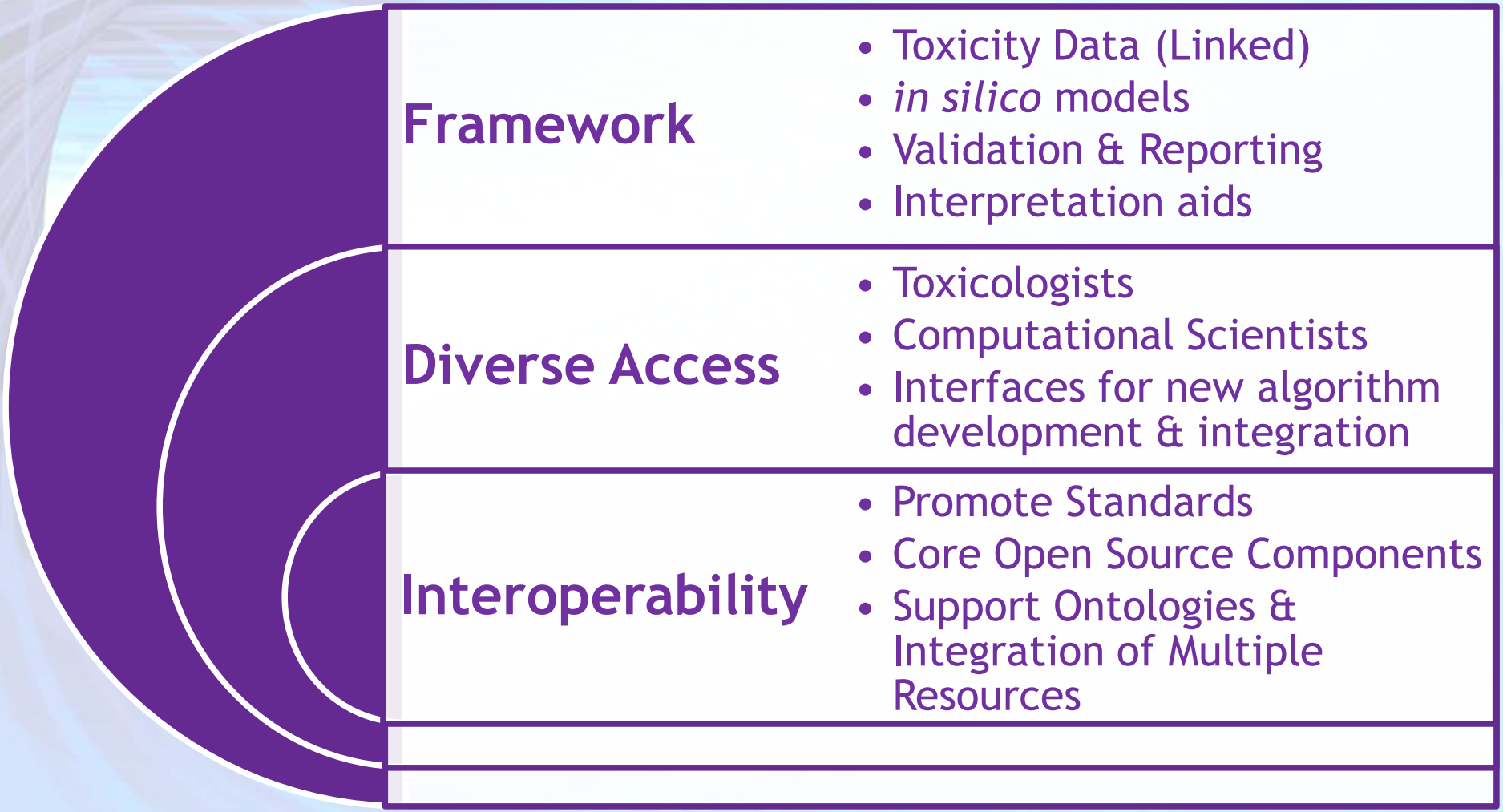
OpenTox Framework



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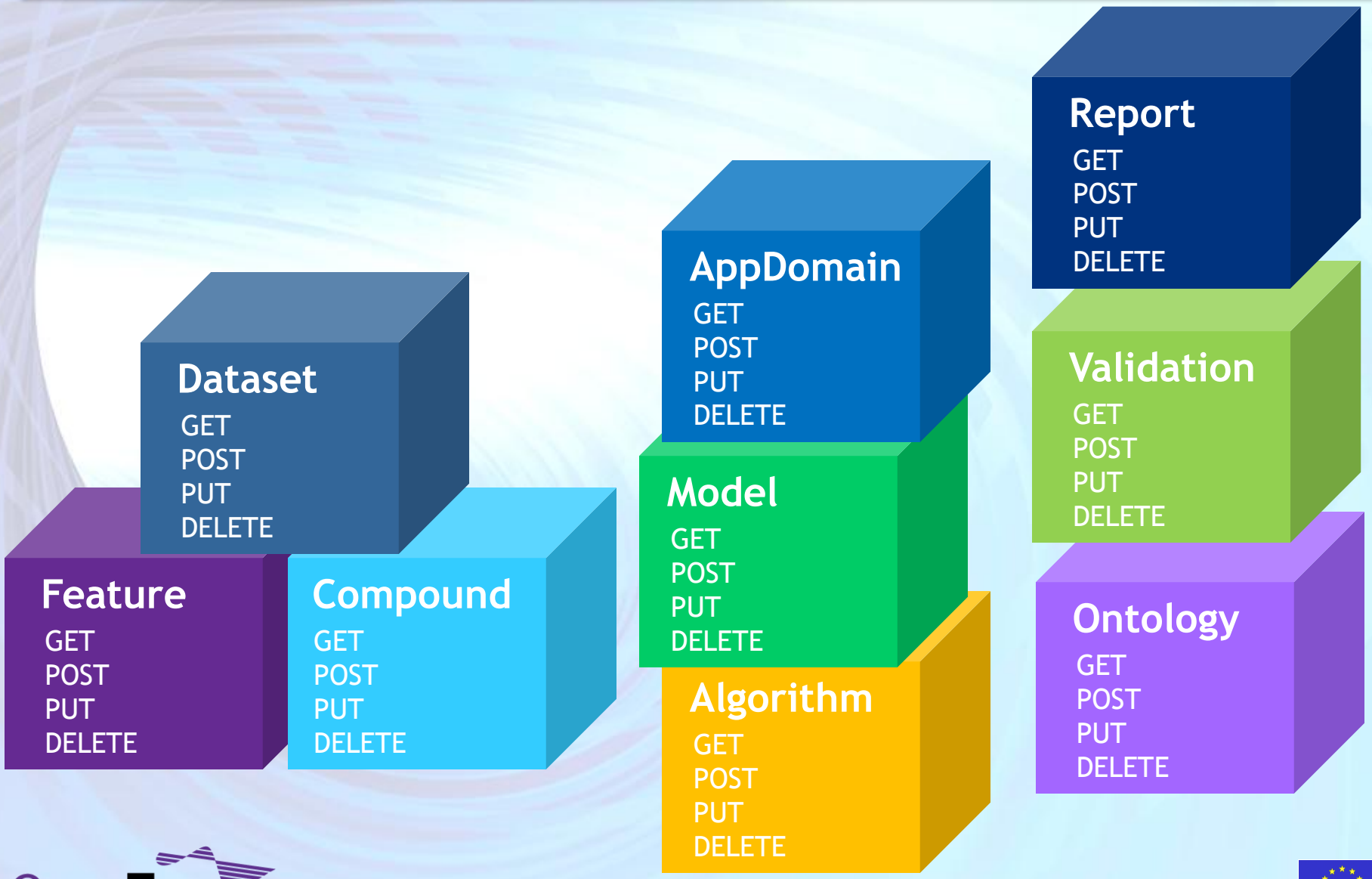
Overview of Application Programming Interfaces



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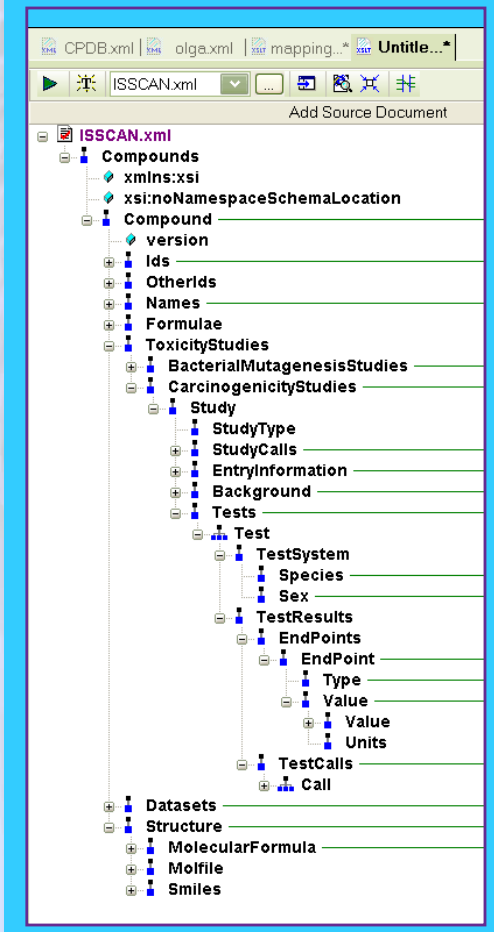
Toxicological Endpoint Ontology Development

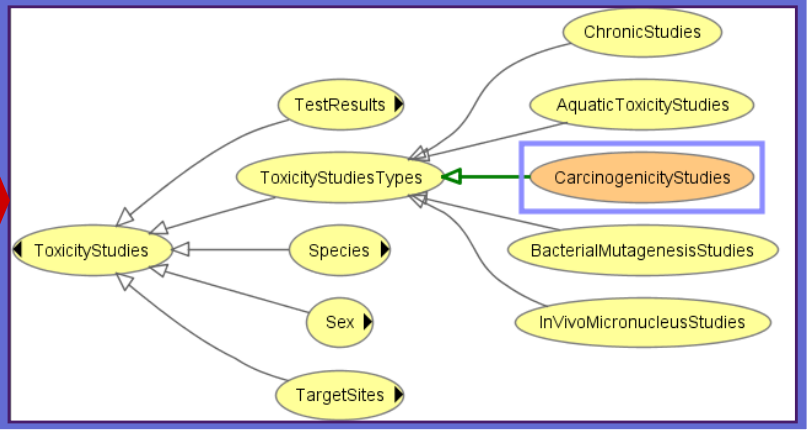
ToxML schema



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

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

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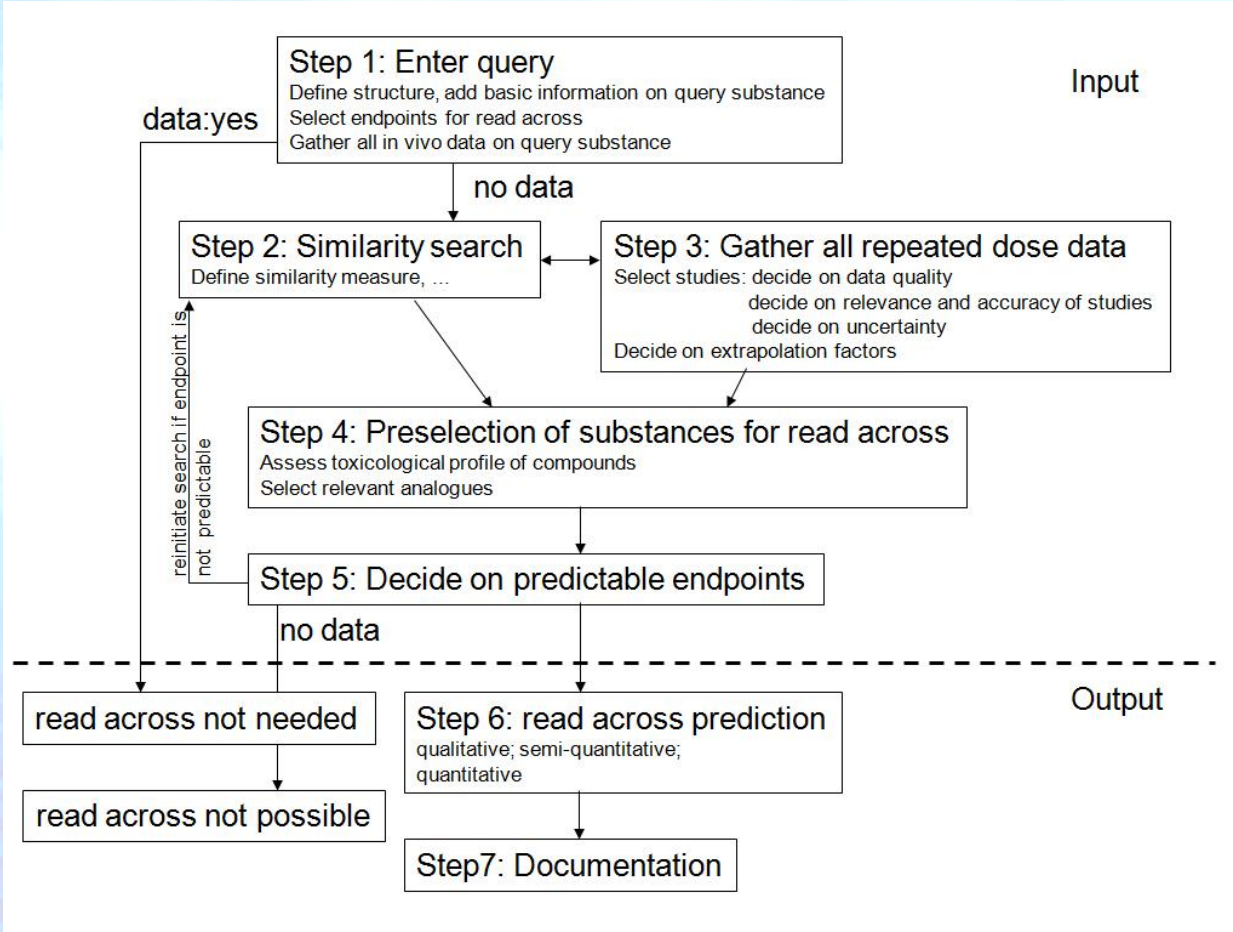
OpenTox Read Across Use Case

Read Across for Repeated Dose Toxicity



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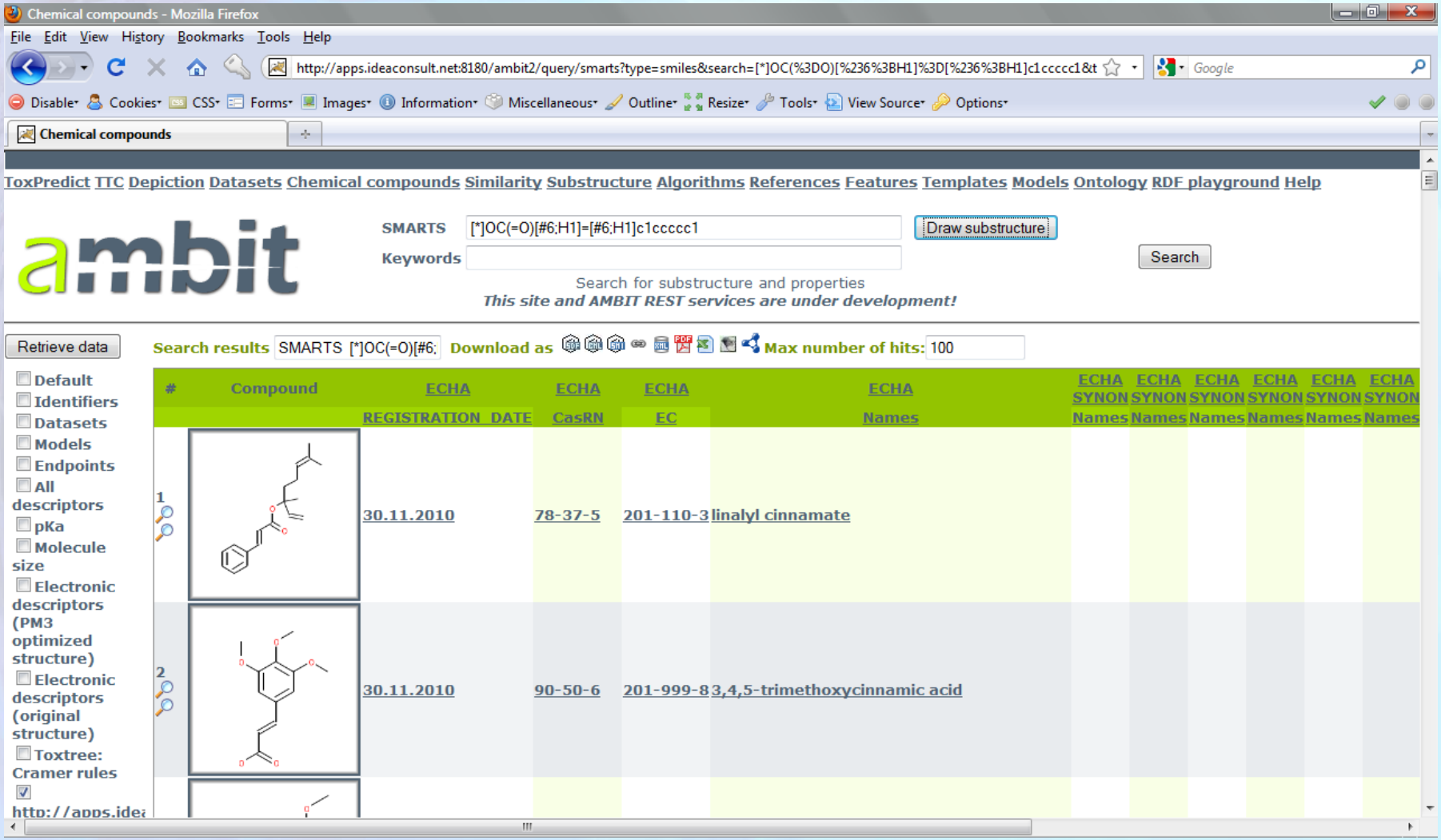
Use Case development led by Sylvia Escher, Fraunhofer Institute

OpenTox: Databases



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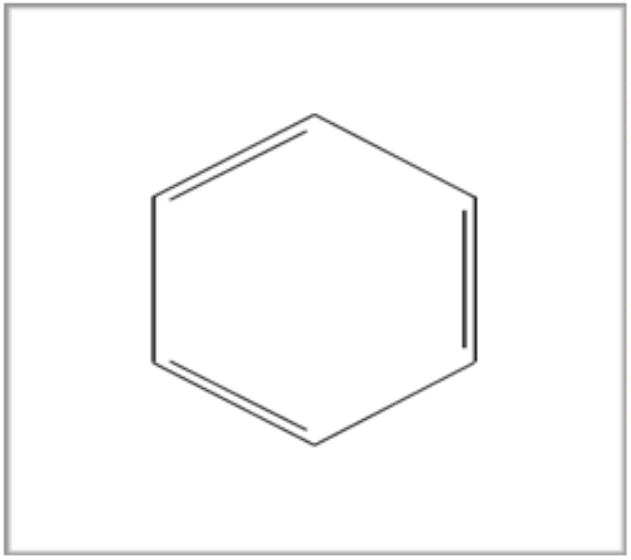
ToxPredict

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

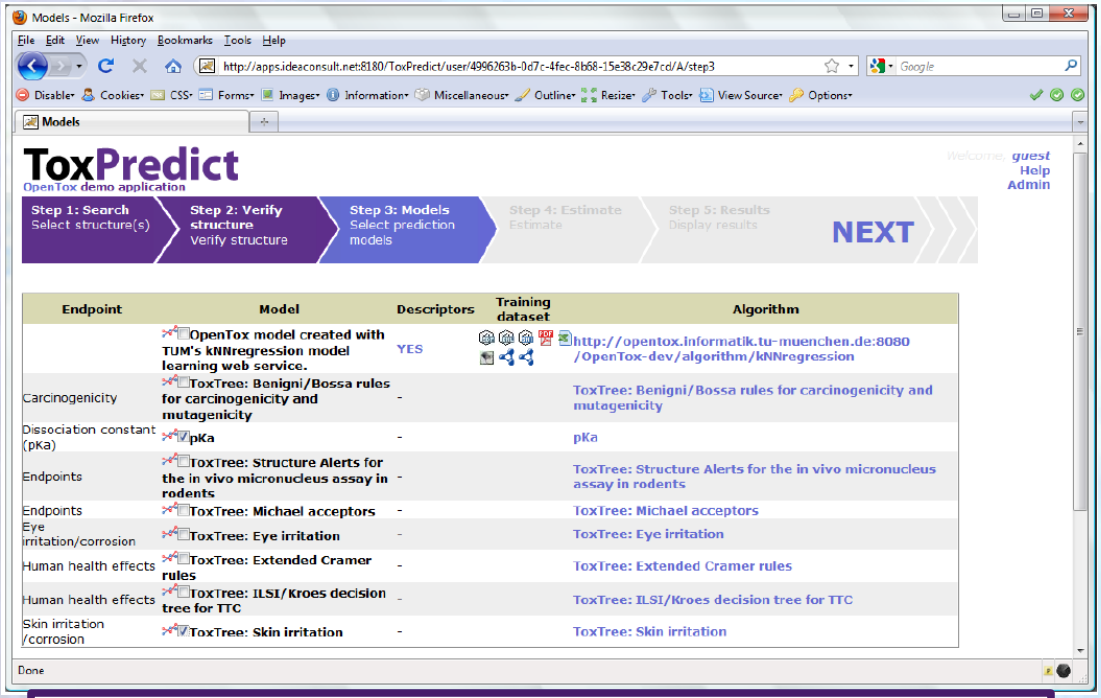


CAS RN	71-43-2
EINECS	200-753-7
IUPAC name	benzene
Synonym	(6)annulene; benzine; Benzol; Benzolene; bicarburet of hydrogen; carbon oil; Coal naphtha; cyclohexatriene; mineral naphtha; motor benzol; nitration benzene; Phene; Phenyl hydride; pyrobenzol.
Synonym	21742.0
Synonym	Benzene
Synonym	benzene
Quality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

MolecularWeight MolecularWeight

MW	78.1112

What you can do with it …



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

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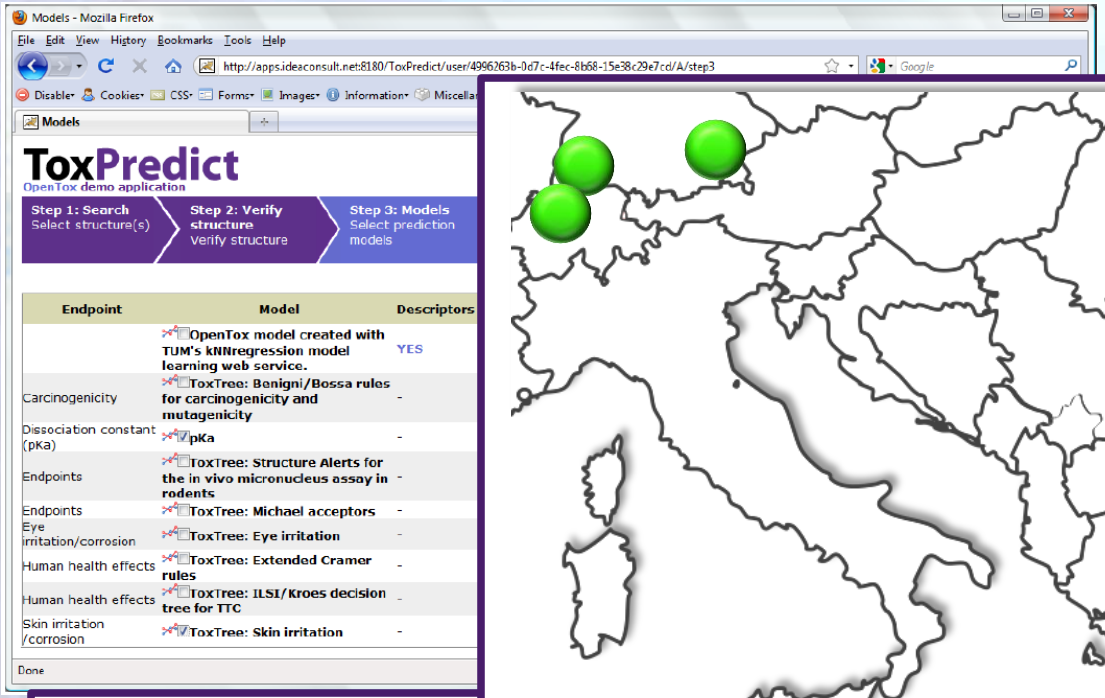
What you can do with it …



Simple building c

applications

methods and

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

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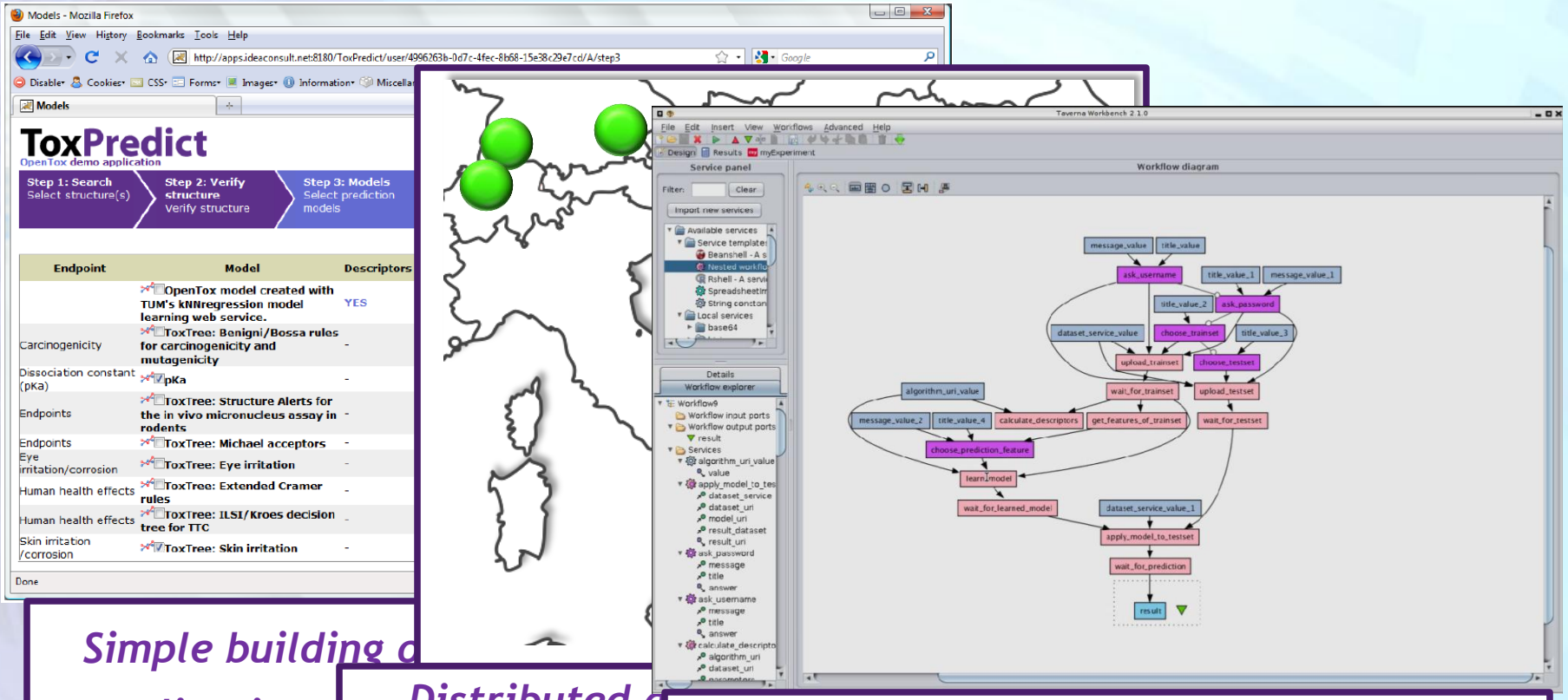
What you can do with it …



Simple building

applications

methods and

Distributed

wide range o

methods

Integration into workflow systems for computational biology

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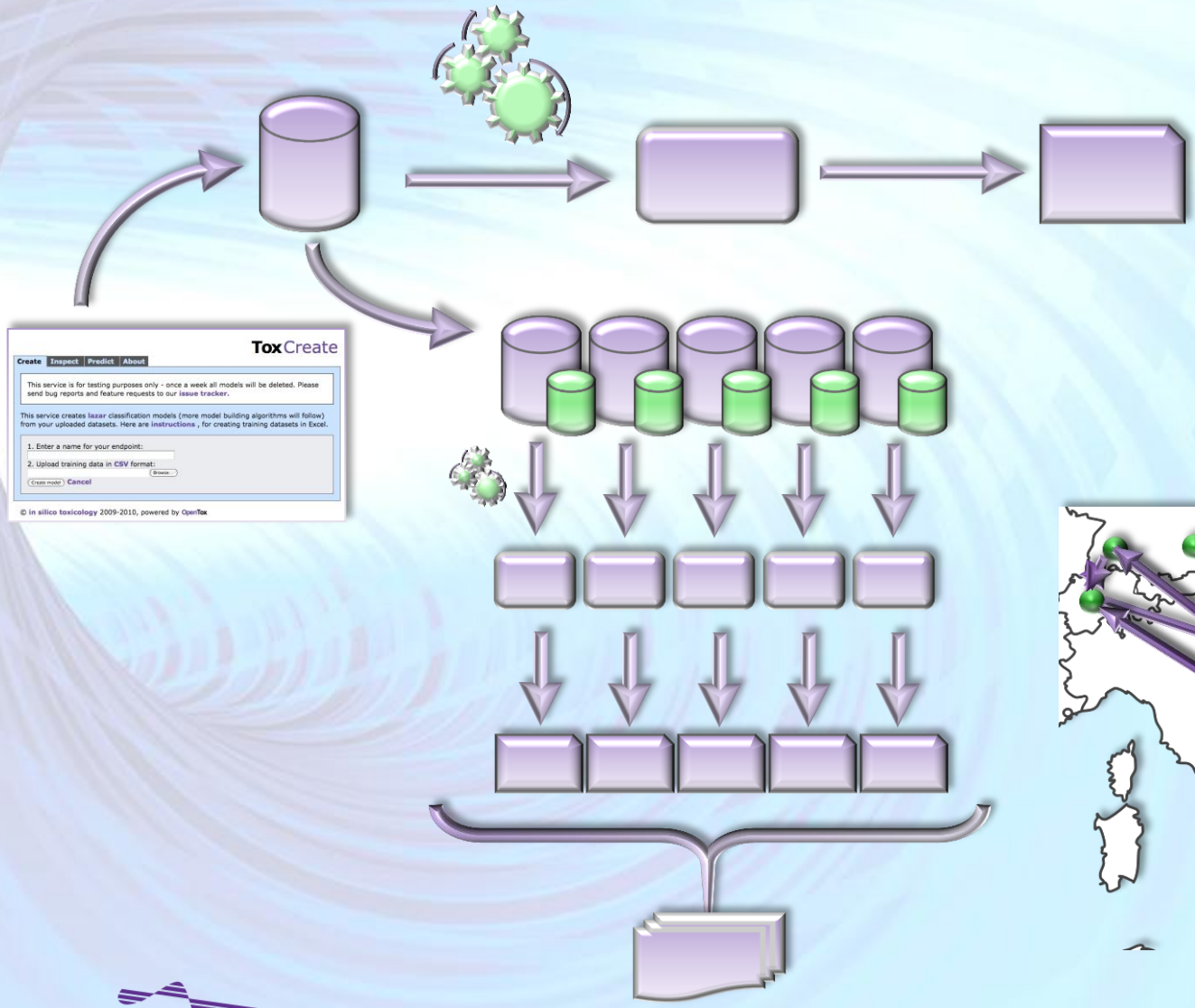
Behind the Scenes of ToxCreate



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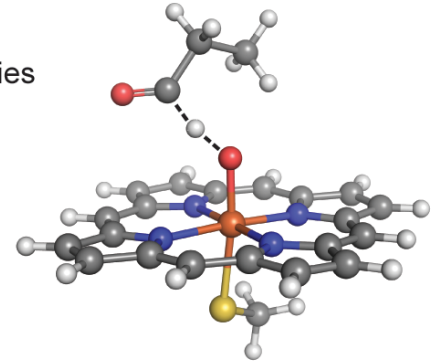
SMARTCyp Service for Predicting Metabolites

Atom Reactivity Library

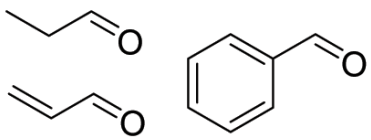
A. Calculate Quantum Chemical Reference Energies

Calculate transition state energies using density functional theory



B. Define SMARTS Rules

Group calculations by fragments and calculate average energies



[CX3H1](=O)[#6]

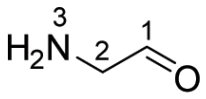
40.2 kJ/mol

SMARTCyp - developed by Patrik Rydberg, University of Copenhagen

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

SMARTCyp

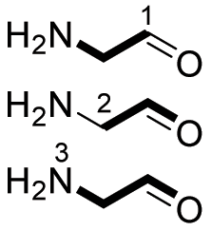
1. Assign Energies By SMARTS matching



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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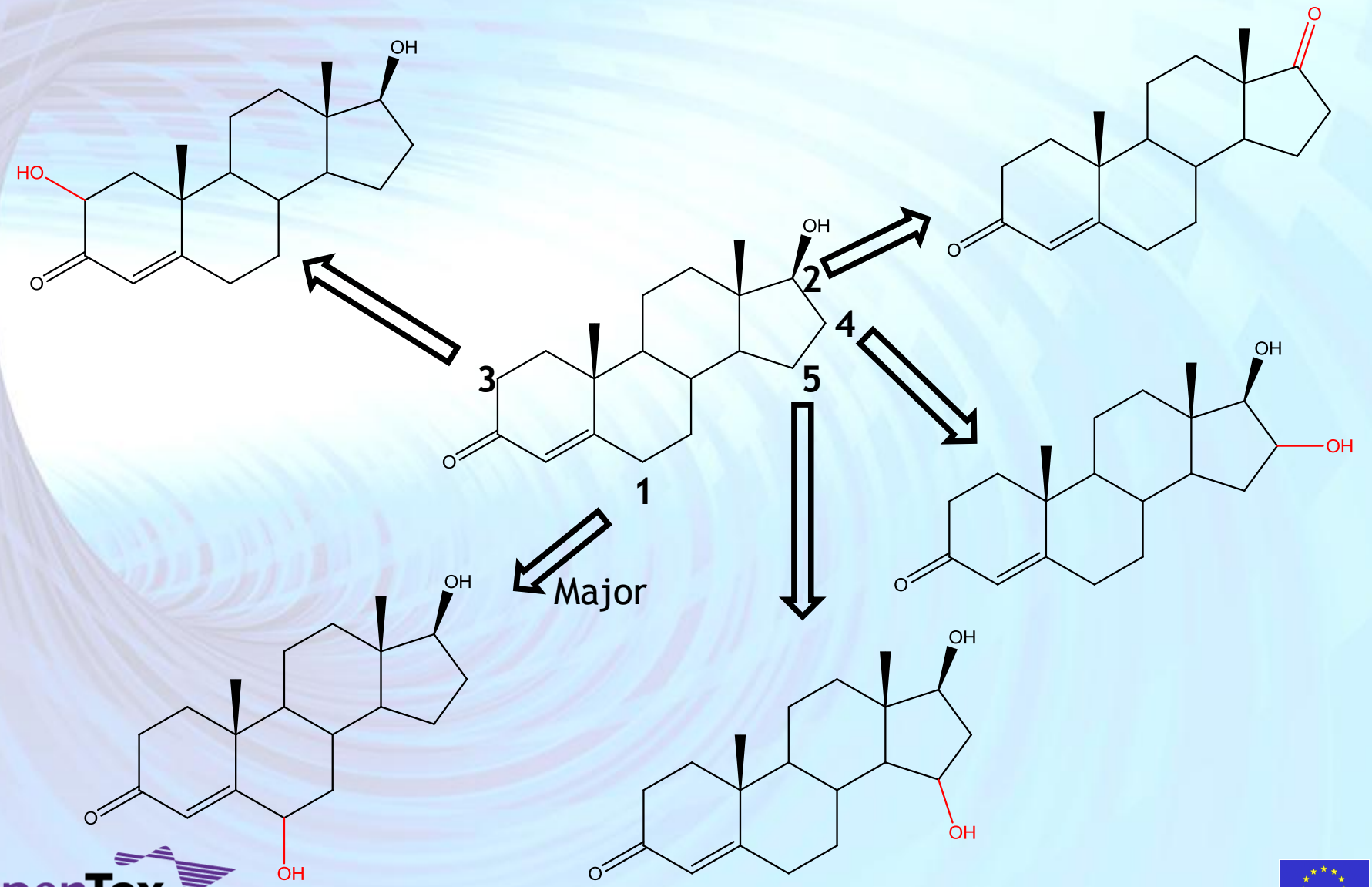
SmartCYP Prediction of Testosterone Metabolites



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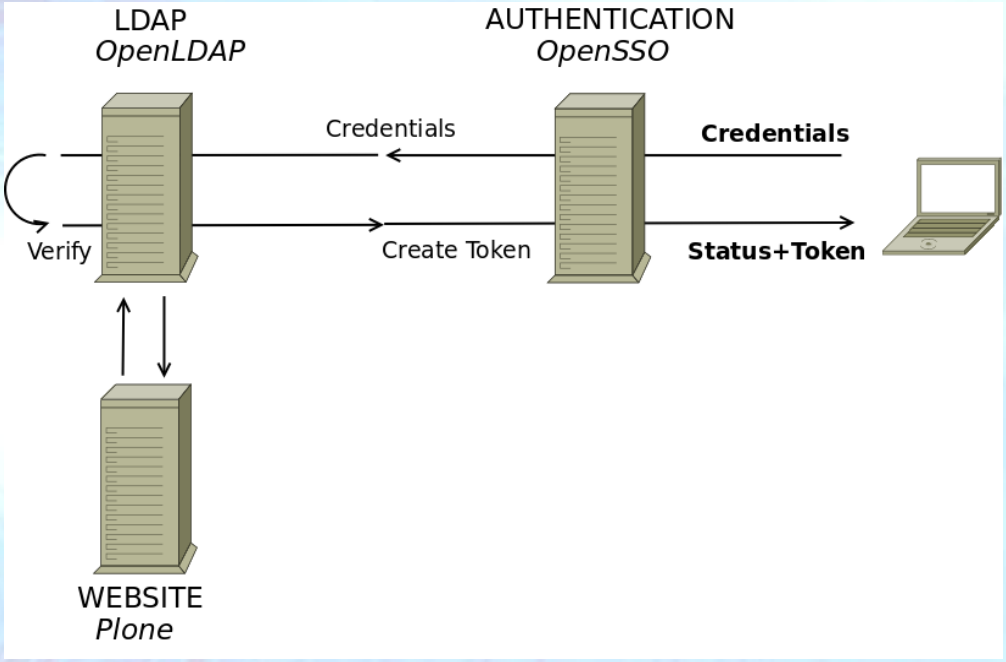
Controlling Access to Confidential Information

- 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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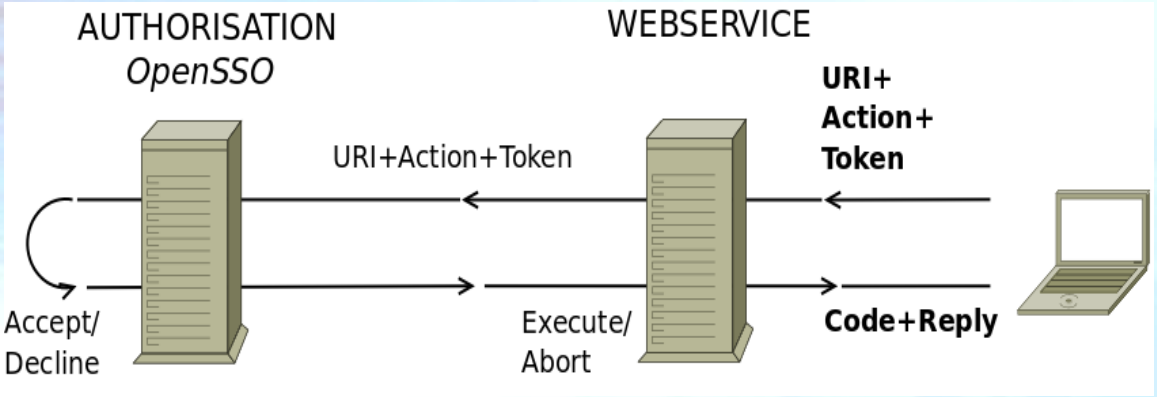
Authorisation



- 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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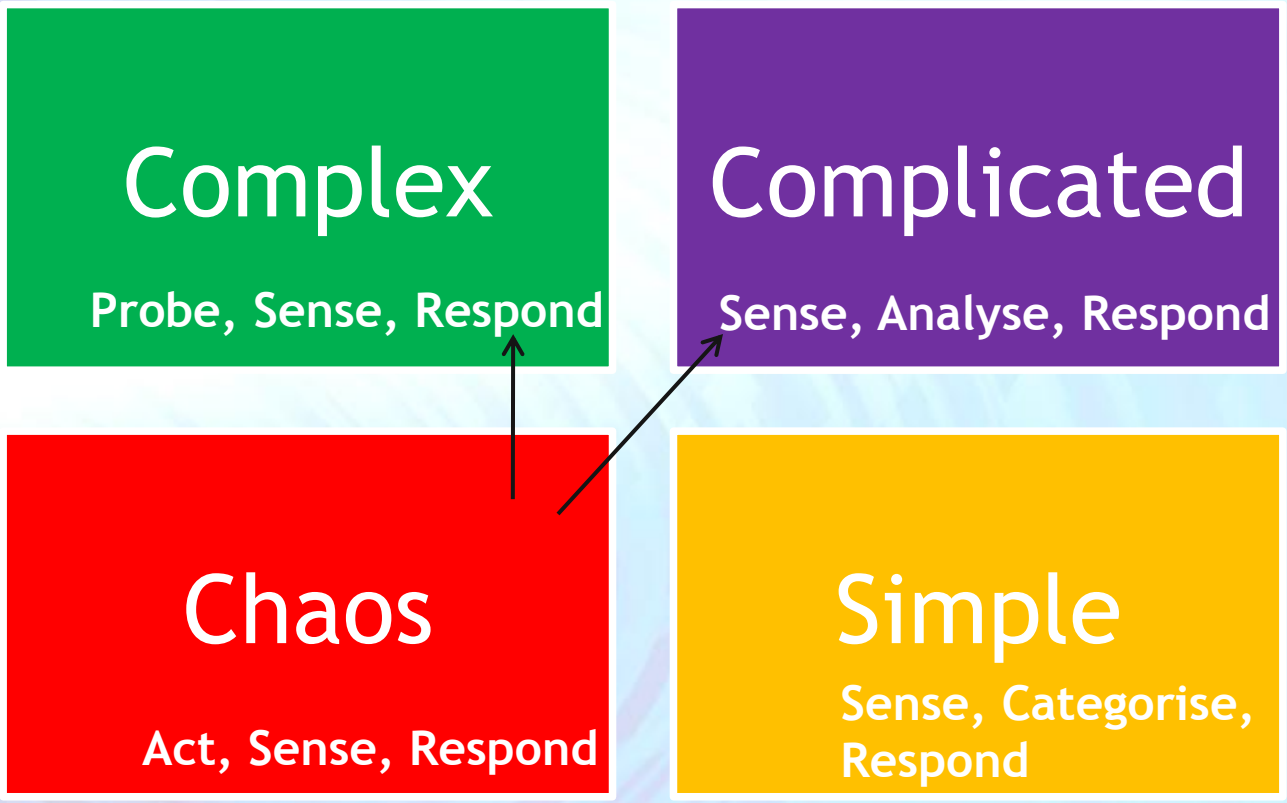
Complexity Context

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,
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From Conservation Project Trip in Caprivi Delta

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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