# Advances in Predictive Toxicology Applications Satisfying Regulatory, Transparency and Interoperablity Requirements

**Mondial Research Group Conference**

**Predictive Human Toxicity and ADME Studies**

***28 January 2010, Brussels, Belgium***


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**OpenTox Project Coordinator**

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SEVENTH FRAMEWORK PROGRAMME

# Our Drivers – Collaboration and Community




From Conservation Project Trip in Caprivi Delta

OpenTox

# Our Drivers – Sustainability and Diversity



Visit with Lions at Mukuni Project, Livingstone, Zambia

OpenTox

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




Visit with Lions at Mukuni Project, Livingstone, Zambia

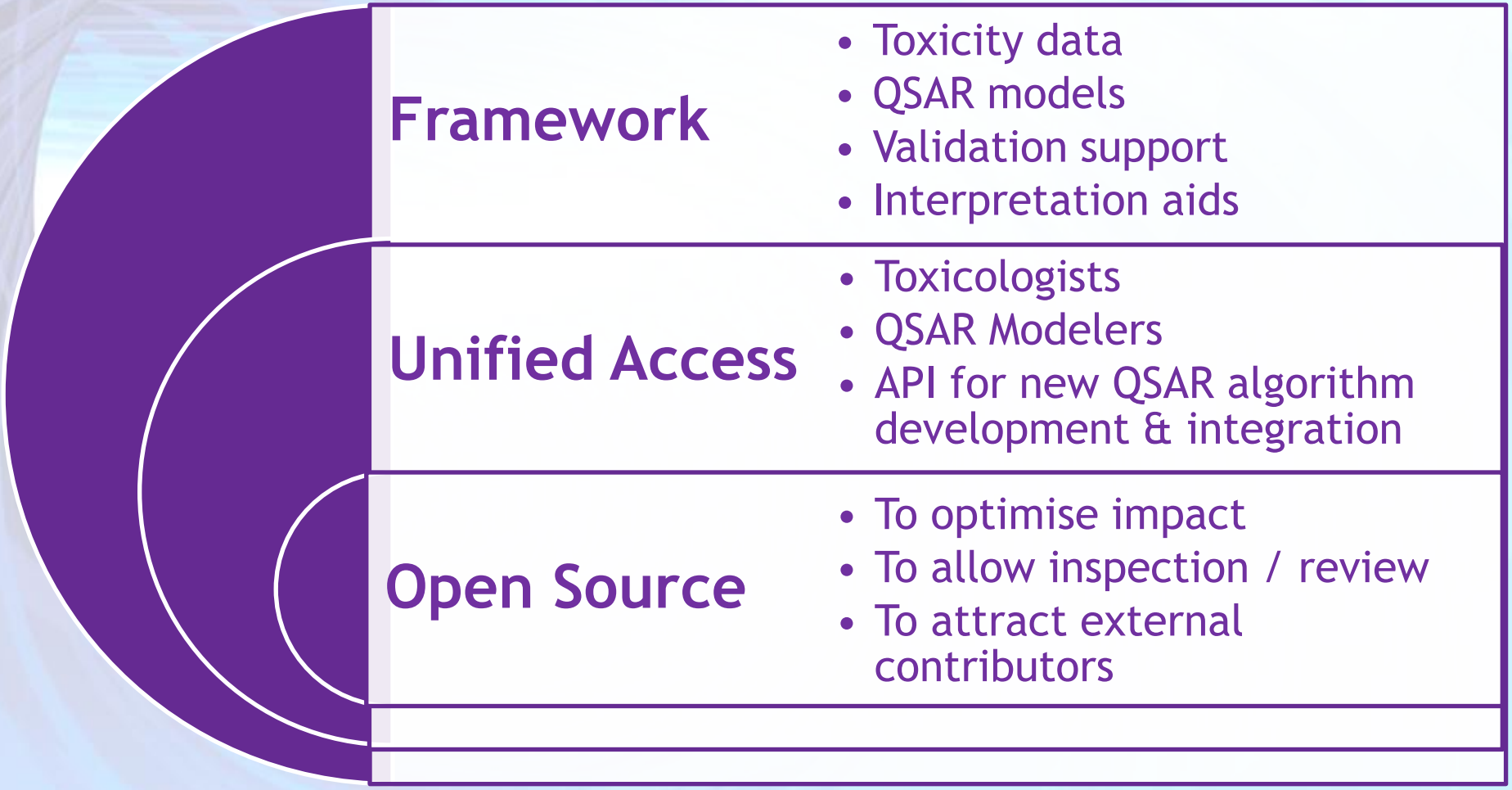
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# Introduction – Challenges to *in silico* Applications (*starting with data driven QSAR approaches…*)

- Toxicity data collected in many different databases using different formats, frequently incompatible with QSAR programs, varying quality
- Many databases lack important information for model development (e.g. chemical structure information)
- Hard to integrate confidential in-house data with public data for model building and validation
- QSAR models have been published in a variety of formats (ranging from simple regression based equations to full-fledged computer programs)
- There is no straightforward integration of predictions from various programs
- No commonly accepted framework for validation of QSAR predictions, many in silico tools provide limited support for reliable validation procedures
- Application, interpretation, & development of models is still difficult for most toxicological experts
- Analysis requires a considerable amount of statistical, cheminformatics and computer science expertise - procedures are labor intensive and prone to human errors
- Lack of algorithm and model transparency, evaluation, extensibility

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# OpenTox Approach



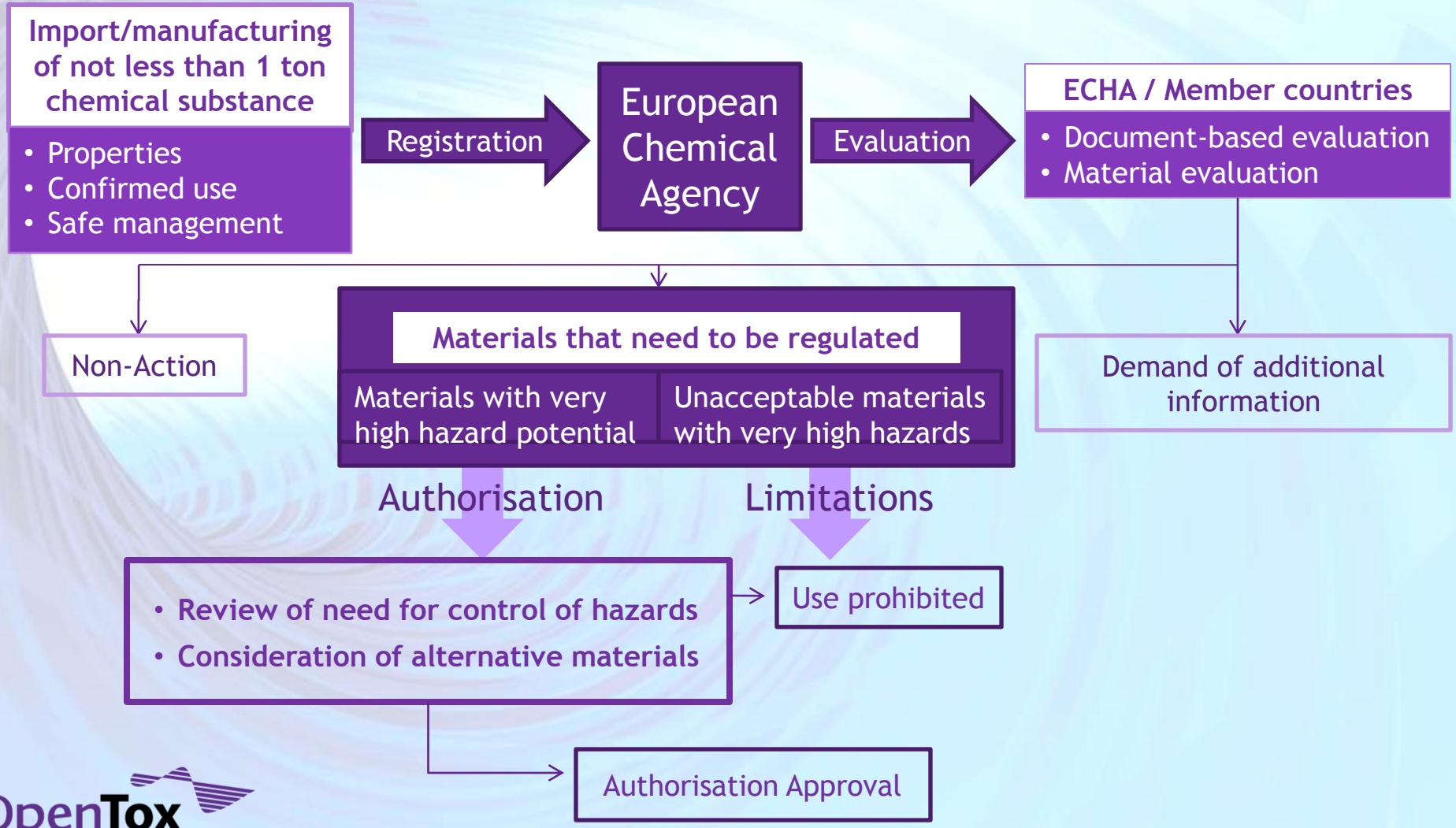

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# REACH




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# REACH registration




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# REACH, QSAR and 3Rs

ECB study showed new regulations will require an estimated 3.9 million additional test animals if no alternative methods are accepted

Same study pointed to possible reduction by using existing experimental data in conjunction with QSAR

Largest number of test animals will be required for chronic and reproductive toxicity, mutagenicity, carcinogenicity endpoints because no alternative *in vitro* assays currently available

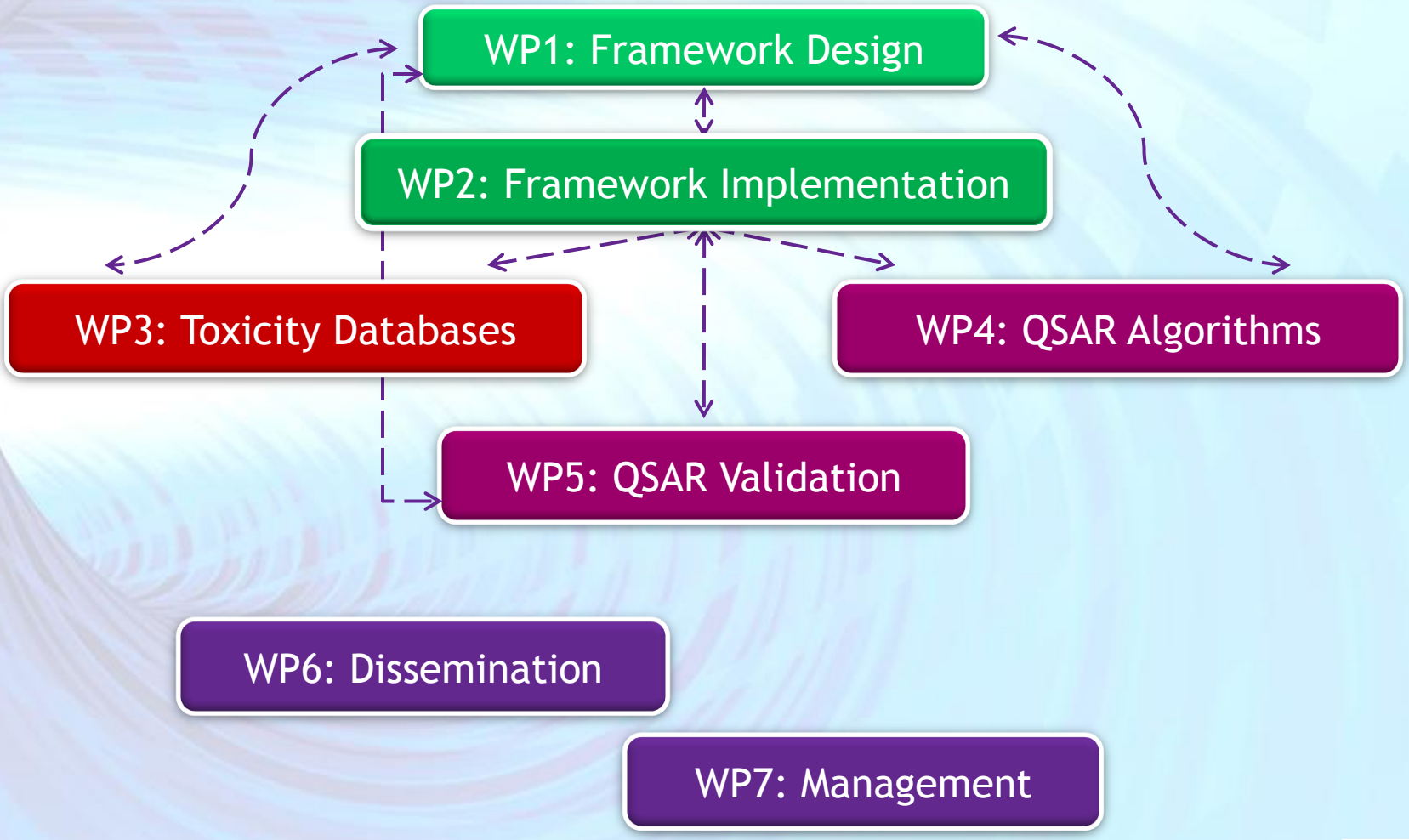
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# Initiation of OpenTox

- **EC FP7 Funded - started September 2008**
- **Initial research has defined:**
  - essential components for framework architecture
  - approach to data access, schema and management
  - use of controlled vocabularies and ontologies
  - web service and communications protocols
  - selection & integration of predictive modeling algorithms
  - interface specifications
- **Analyses of use cases ongoing**

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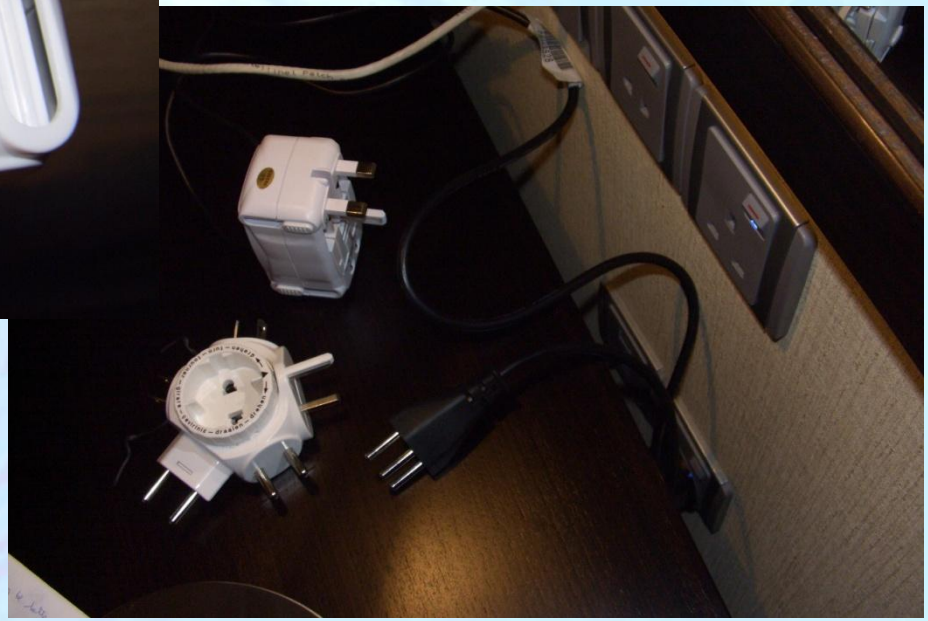
# Introduction - OpenTox Work Packages




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# Interoperability



Adaptor Challenge in Jeddah, 2008

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# Interoperability




Adaptor Solution in Jeddah, 2008

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# Interoperability





Adaptor Solutions in Istanbul, CMTPI 2009

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# OpenTox Framework - definition

- OpenTox is a platform-independent collection of components that interact via well defined language-independent interfaces
- The preferred form of communication between components is through web services (REST)
- OpenTox supports Open Source & “Commercial Software” (Transparency?, What is *Commercial?”)
- OpenTox is committed to the support and further development of Open Standards and ontologies

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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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# OpenTox Framework - Components

## Component Descriptions

- See OpenTox.org site for templates that provide documentation including minimum requirements and dependency tracking

## Component Categories

- Prediction
- Descriptor Calculation
- Data Access
- Report Generation
- Validation
- Integration

## Initial Components

- Rumble
- Toxmatch
- Toxtree
- iSar
- lazar
- AMBIT
- FreeTreeMiner
- LibFminer
- gSpan'
- MakeMNA
- MakeQNA
- MakeSCR

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# OpenTox Framework - Interfaces

The initial specifications for the OpenTox Application Programming Interfaces (APIs) have been defined and made available on the OpenTox website

The objects specified are Endpoint, Structure, Structure Identifiers, Feature Definition, Feature, Feature Service, Reference, Algorithm, Algorithm Type, Model, Dataset, Validation Result, Applicability Domain, Feature Selection, and Reporting

The Representational State Transfer (REST) architecture is being used as the web service approach for the communication between components in a distributed system

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# OpenTox Framework - Interfaces

Model developers will benefit from the OpenTox API because it allows an easier integration, testing and validation of new algorithms and resources

New techniques can be more easily tested with relevant toxicity data and compared to the performance of benchmark algorithms

Agile Programming, Use Case driven iterative development procedures being pursued

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# OpenTox Framework - API 1.1

- Goto OpenTox website -> Development  section -> APIs for detailed public specification (… and to comment on, make proposals)
- Assume OpenTox components are web services with a REST interface (en.wikipedia.org/wiki/Representational_State_Transfer) .
- Parameters are posted with a "Content-Type:application/x-www-form-urlencoded" HTTP header. Square brackets (e.g. **compound_uris[]**) indicate that a list of arguments is expected.

  **Example:** curl -X GET http://{server}/dataset?compound_uris[]={compound_uri1}&compound_uris[]={compound_uri2})

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# OpenTox Framework - API 1.1

- The default OpenTox format is RDF/XML (with exception of the compound API), but service developers may support additional formats. You can request them, by specifying the MIME type in the "Accept" and "Content-Type" HTTP headers.

  Example: Request a compound in SDF format:

  curl -X GET -H "Accept:chemical/x-mdl-sdfile" http://{server}/compound/{id}

  Example: Submit a compound in InChI format:

  curl -X POST -H "Content-Type:chemical/x-inchi" --data-binary "InChI=1S/C5H10/c1-2-4-5-3-1/h1-5H2" http://{server}/compound

  Example: Create a new dataset:

  curl -X POST -H "Content-Type:application/rdf+xml" --data-binary@my_data_file.rdf http://{server}/dataset

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# OpenTox Framework - API 1.1

- Initial versions of APIs completed for:
  - Compound
  - Algorithm
  - Dataset
  - Model
  - Task
  - Validation
- Others on reporting, ontology, authentication are more work in progress
- First two development interations ca. 5 months completing end of November 09. Moving to 6 weeks iterations in early 2010. Initial prototypes release end of February 2010. Further iterations and releases based on additional use case-driven development accompanied by further API updates...workshops...

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# Ontology and Data - Concept and Goals

| | |
|---|---|
| OpenTox Must | • define the ontology & controlled vocabulary<br>• standardize and organize high-level concepts, chemical information and toxicological data |
| Needs | • distributed services exchanging communications<br>• unambiguous interpretations of the meaning of any terminology & data they exchange between each other |
| Supports | • creation of dictionaries and ontologies describing relations between chemical and toxicological data and experiments<br>• development of novel techniques for the retrieval and quality assurance of toxicological information |

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# Ontology and Data - Endpoints

## OpenTox toxicity data infrastructure

- The OpenTox toxicity data infrastructure includes the toxicological end points for which data are required under the REACH regulation
- In current toxicological testing, these endpoints are addressed by both *in vitro* and *in vivo* experiments carried out according to OECD guidelines

## REACH toxicological endpoints

- Skin irritation
- Skin corrosion
- Eye irritation
- Dermal sensitisation
- Mutagenicity
- Acute oral toxicity
- Acute inhalative toxicity
- Acute dermal toxicity
- Toxicokinetics
- Repeated dose toxicity (28 days)
- Repeated dose toxicity (90 days)
- Reproductive toxicity screening
- Developmental toxicity
- Two-generation reproductive toxicity study
- Carcinogenicity study

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# Ontology and Data – Public Data Sources

- Textual databases eg. IARC, NTP
- Sources of machine readable files (such as .sdf)
  - that include both structures and data
  - and that can be immediately used by modellers for (Q)SAR analyses in the OpenTox platform e.g., DSSTox, ISSCAN, AMBIT, REPDOSE
- Curated Data with REACH relevance eg. ISS's databases on Rodent Carcinogenicity; Carcinogenic Potency TD50; Ames test Mutagenicity; *in vivo* Micronucleus in Rodents
- Large and quite complex databases on the Internet eg. PubChem, ACToR
- US EPA's ToxCast Data
- FDA Data

# Ontology and Data - Schema

## ToxML public schema initiative led by Leadscope

Two-fold objective of :

- supporting broadly encompassing and meaningful representations of toxicology experiments, with hierarchical schemes including various levels of complexity
- indexing the data with the chemical structures, so as to permit the widest range of chemical biological interrogations of the database

## OECD harmonized templates

Corresponding to IUCLID5 XML schemas

- contains schemas for all the various endpoints of regulatory relevance
- required for regulatory reporting

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# Ontology and Data - Mappings

The ISSCAN carcinogenicity database was fully mapped to ToxML's XSD schema and partially to the OECD-Harmonized Templates schema

Additional mapping exercises included those for aquatic toxicity (EPAFHM in DSSTox), repeated doses toxicity (REPDOSE), endocrine disruptors (NCTRER in DSSTox), and a second carcinogenicity database (CPDBAS in DSSTox)

The ISS *in vivo* micronucleus and Bacterial mutagenesis databases and the RepDose database were fully mapped to ToxML XSD schema, with in each case valid XML documents (against ToxML XSD schema) obtained

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# Ontology and Data – Evaluation Conclusion

- ToxML
  Seems to be closer to the needs of building data architecture aimed at scientific computing, but adaptations and extensions for future development may be necessary. It will be supported by OpenTox for interoperable data communications between services.

- OECD harmonized templates, IUCLID5 XML schemas
  Are more suitable for textual archives than for scientific computing. OpenTox needs to also support it primarily for reporting purposes.

- Critical need to collaborate to extend ToxML cohesively across FP7, OpenTox, IMI eTox, FDA, US EPA, Leadscope, Lhasa, industry .. align with Ontology Development, OBO Foundry, SNOMED, Pistoia Alliance, COLIPA-FP7 initiative, etc to create “fit for purpose” standardised ontologies

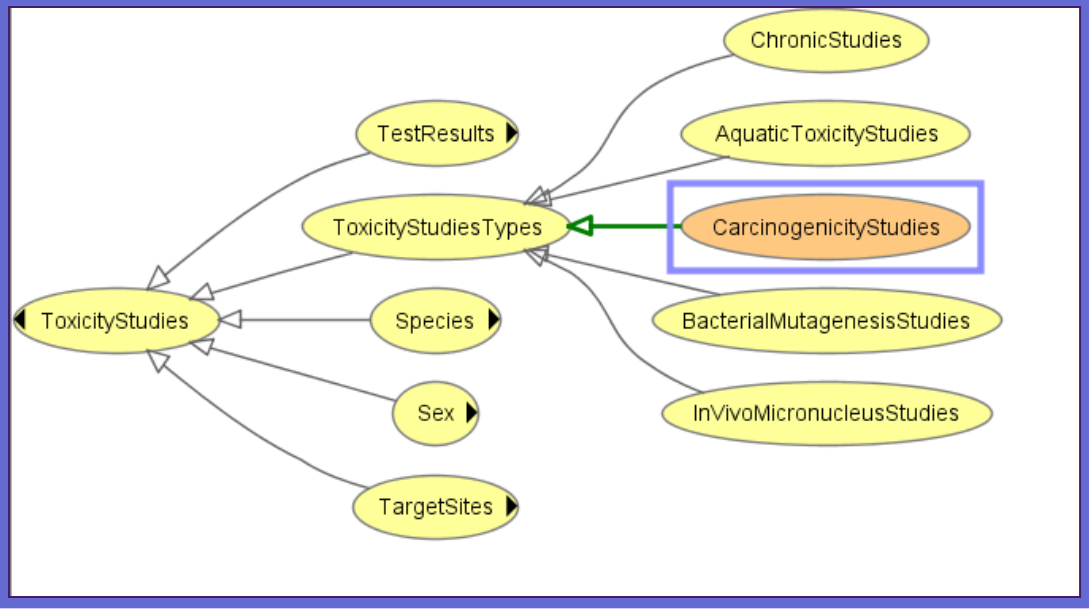
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# Ontology For Toxicological Endpoints

Ontologies are controlled vocabularies enriched with relations between terms

## Starting from 5 toxicological endpoints

- defining classes in the ontology,
- arranging the classes in a taxonomic hierarchy




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# Toxicological Data ontology development

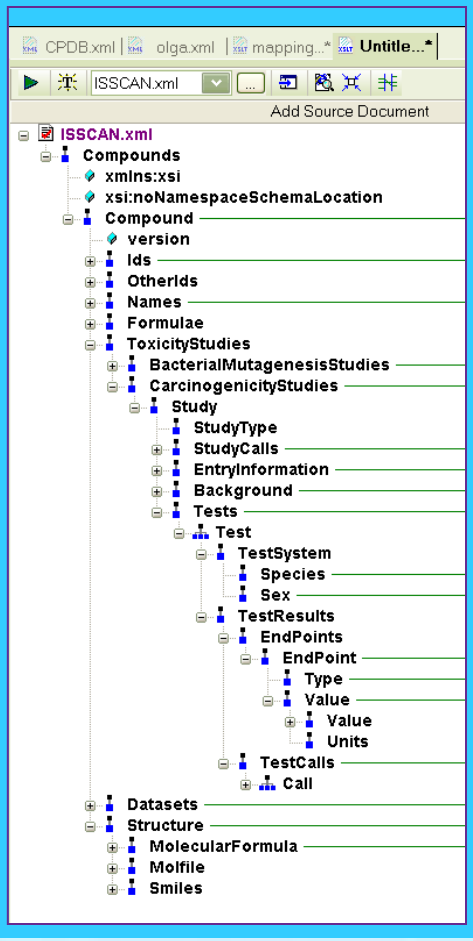
Other publically available resources: DSSTox, GoReni (ITEM), ISSCAN ...

Protégé, open source OWL (Web Ontology Language ) editor
protege.stanford.edu

OpenTox Toxicological Data Ontology

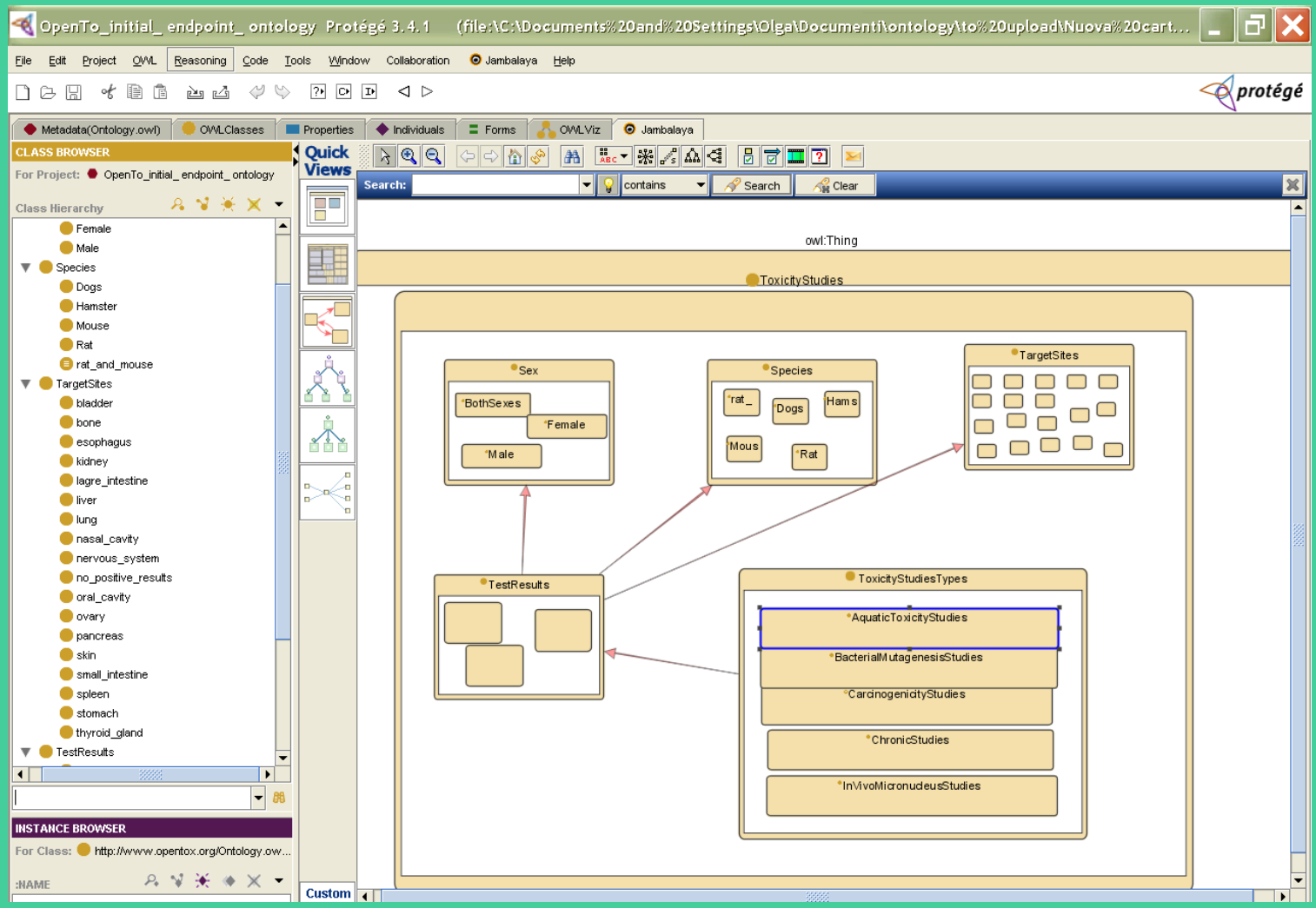
Re-use of terms defined in neighbouring ontologies (e.g., OBO)

## ToxML schema




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# OpenTox endpoints ontology example in Protègè




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# OpenToxipedia

- New OpenTox Community-based Vocabulary Initiative
- **Resource Location:** www.opentox.org/opentoxipedia
- OpenTox is supporting the creation and curation of OpenToxipedia, a community-based curated predictive toxicology knowledge resource. Members of the community are welcome to provide entries, suggested definitons and edits or additional information to entries in the resource
- OpenToxipedia provides a Vocabulary Resource of toxicology terminology
- Intention to extend to cover new emerging vocabulary for alternative *in vitro* toxicology assays
- Include vocabulary meeting regulatory reporting requirements in alternative testing

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# Validation

An objective validation framework is crucial for the acceptance and the development of QSAR models. The risk assessor needs reliable validation results to assess the quality of predictions.

Model developers need this information:

- to avoid the overfitting of models
- to compare new models with benchmarked techniques
- to get ideas for the improvement of algorithms (e.g. from the inspection of misclassified instances).

Validation results can also be useful for data providers as misclassifications point frequently to flawed database entries. OpenTox is actively supporting the OECD Principles for QSAR Validation so as to provide easy-to-use validation tools for algorithm and model developers.

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| | OECD Principle | OpenTox addresses by... |
|---|---|---|
| 1 | Defined Endpoint | providing a unified source of well defined and documented toxicity data |
| 2 | Unambiguous Algorithm | providing unified access to documented models and algorithms as well as to the source code of their implementation |
| 3 | Defined Applicability Domain | integrating tools for the determination of applicability domains and considering these during the validation of (Q)SAR models |
| 4 | Goodness-of-fit, robustness and predictivity | providing scientifically sound validation routines for the determination of these measures |
| 5 | Mechanistic interpretation (if possible) | providing tools for the prediction of toxicological mechanisms, for the web-mining for toxicological information, and data resources with references relevant to particular (Q)SARs and datasets |

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# User Requirements - Use Cases

- OpenTox needs to be very flexible to meet individual needs
- A Use Case driven development & testing approach
- Cases may be submitted through www.opentox.org website for evaluation for inclusion in development planning
- 3 hierarchical classes of Use Cases:
  1. **Collaboration / Project Level** e.g. 3-month development project
  2. **Application Level** .carry out a REACH-compliant risk assessment for group of chemicals
  3. **Task Level** e.g. Given an endpoint – and a dataset for a chemical structure category for that endpoint – develop and store a predictive model resource for a chemical space

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# OpenTox Use Cases - Class 1 level

**Category A - Collaboration Initiation**

1.A.1 Given a Predictive Toxicology Request for Proposal (RFP), prepare and return a Proposal

1.A.2 Given a Predictive Toxicology Proposal, carry out Setup of OpenTox Collaborative Project

**Category B - Collaboration Operation**

1.B.1 Run a Collaborative *in silico - in vitro* Predictive Toxicology Project

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# OpenTox Use Cases - Class 2 level

**Category A Prioritization**

2.A.1 Given a set of *in vitro* data predict *in vivo* data

2.A.2 Given a set of chemicals and endpoint(s) prioritise selection of *in vitro* assays

2.A.3 Given a set of chemicals prioritise subsets for *in vitro* and/or *in vivo* testing

2.A.4 Decision tree proposed by ILSI Europe to decide whether substances can be assessed by the TTC approach (Kroes et al., Food and Chemical Toxicology, 42, p76, 2004)

**Category B Risk Assessment**

2.B.1 Given a chemical generate a REACH risk assessment report

**Category C Resource Integration and Management**

2.C.1 Integration of multiple data sources and resources for a predictive toxicology model

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# OpenTox Use Cases - Class 3 level (a)

**Category A Prediction**

3.A.1 Given a chemical structure, predict an endpoint
3.A.2 Given a set of endpoint data, develop and store a predictive model
3.A.3 Develop a predictive model for the SVM algorithm
3.A.4 Maxtox. Predicting Toxicity using similarity scores
3.A.5 Given set of data for endpoint, develop, internally validate and store multiple predictive models
3.A.6 Read Across for chronic toxicity
3.A.7 Create a consensus-based predictive model
3.A.8 Create a Category for a Complex Endpoint (Repeated Dose)
3.A.9 Determine the Applicability Domain of a Prediction Model

**Category B Descriptors**

3.B.1 Given a set of chemicals, select a set of descriptors for modelling an endpoint

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# OpenTox Use Cases - Class 3 level (b)

**Category C Validation**

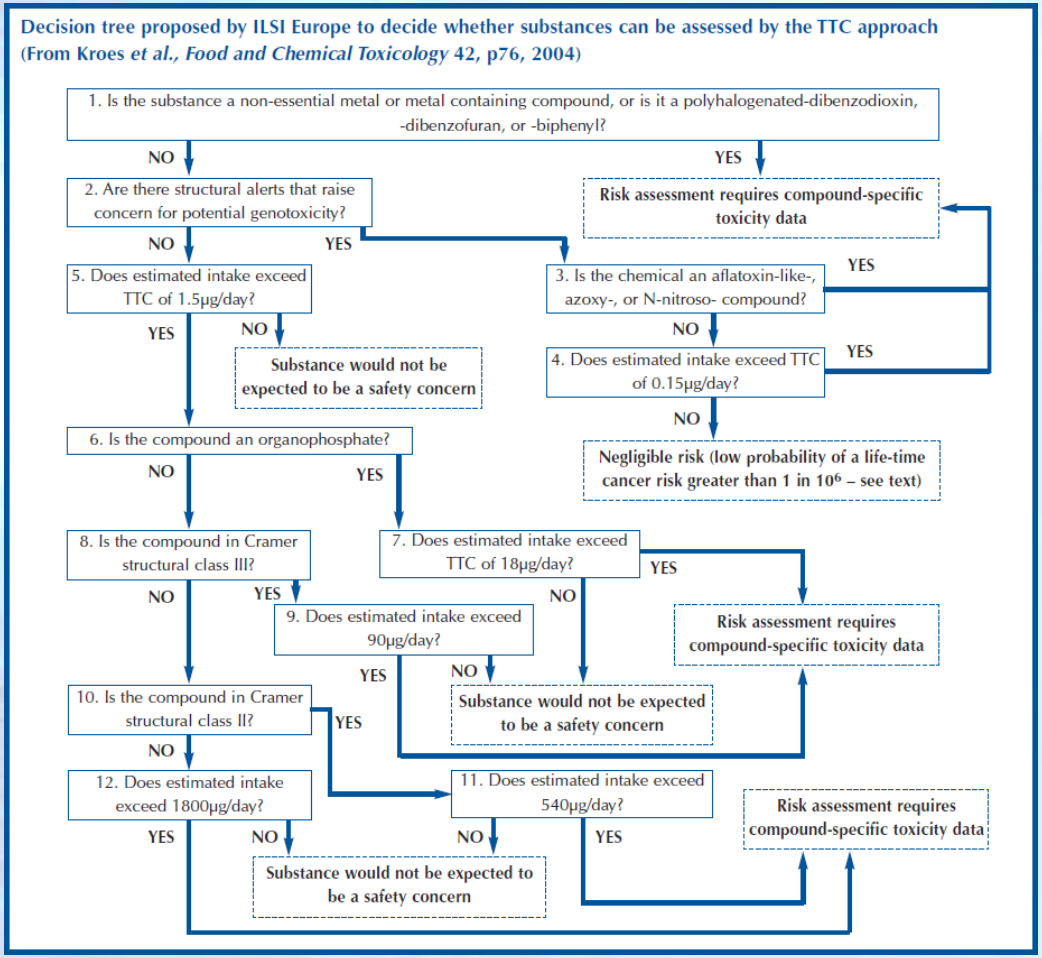
3.C.1 Validate an SVM-based QSAR model
3.C.2 Validate a prediction model
3.C.3 Integrating and validating a new Algorithm
3.C.4 Compare performance of different models / algorithms
3.C.5 Given an external set of data for an endpoint, validate multiple predictive models

**Category D Reporting**

3.D.1 Generate a QMRF report
3.D.2 Generate a QPRF report
3.D.3 Create a report for a consensus model prediction

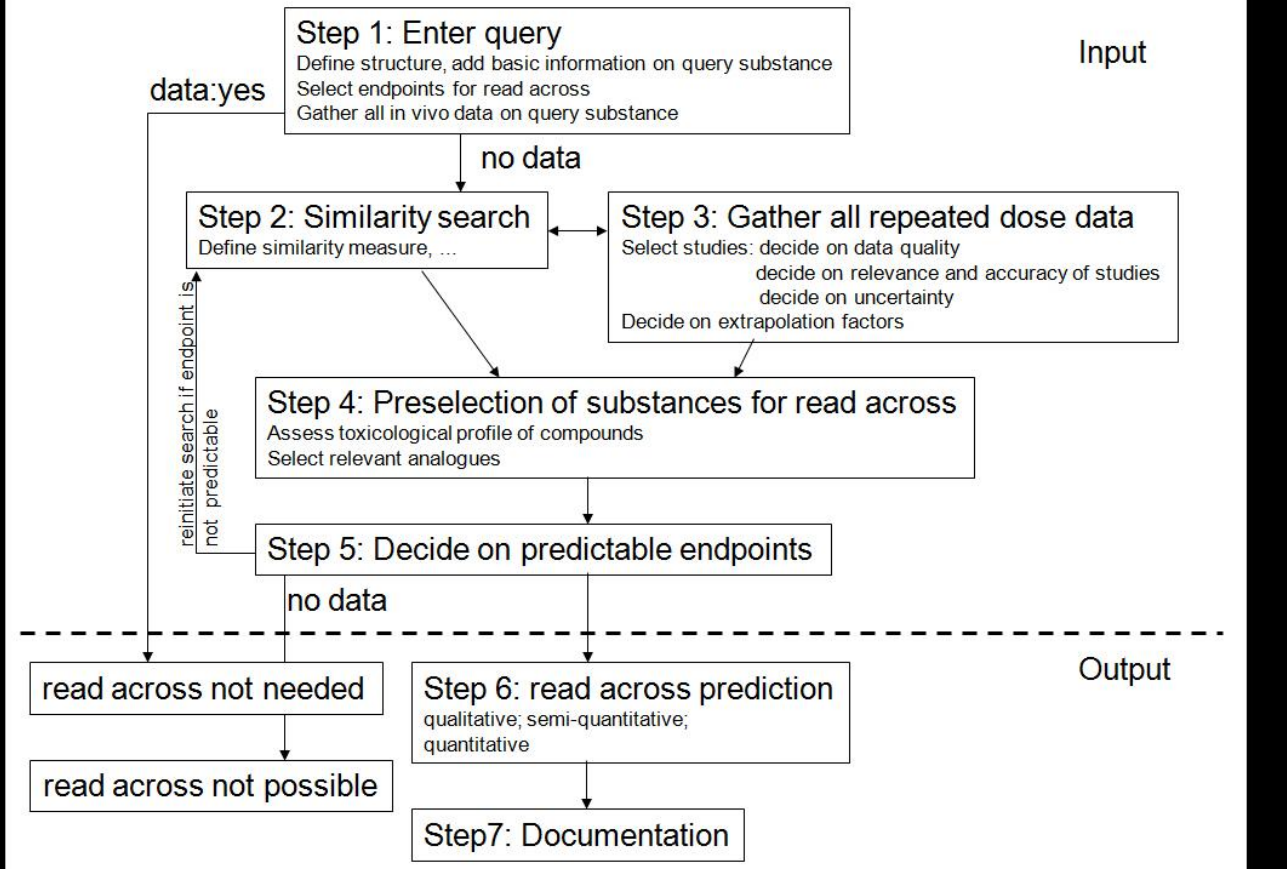
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# OpenTox Use Case - implement Threshold of Toxicological Concern (TTC) using ILSI decision tree guidelines




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# OpenTox Use Case – Read Across for Repeated Dose Toxicity




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# OpenTox Use Case - given a structure, predict endpoints

OpenTox data resources are searched for chemical id number or structure

The structure is checked for chemical correctness and number of molecules

Clean up, conversion to 3D, valences saturated with hydrogen atoms, partially optimized with molecular mechanics

A check on the chemical correctness is made (bond distances, charges, valences, etc.)

An image of the molecule is displayed, with the results of structure check and clean-up. If serious problems with the structure are found, the user is asked if they want to continue, or if appropriate, the process is terminated automatically with an error message.



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# OpenTox Use Case - given a structure, predict endpoints

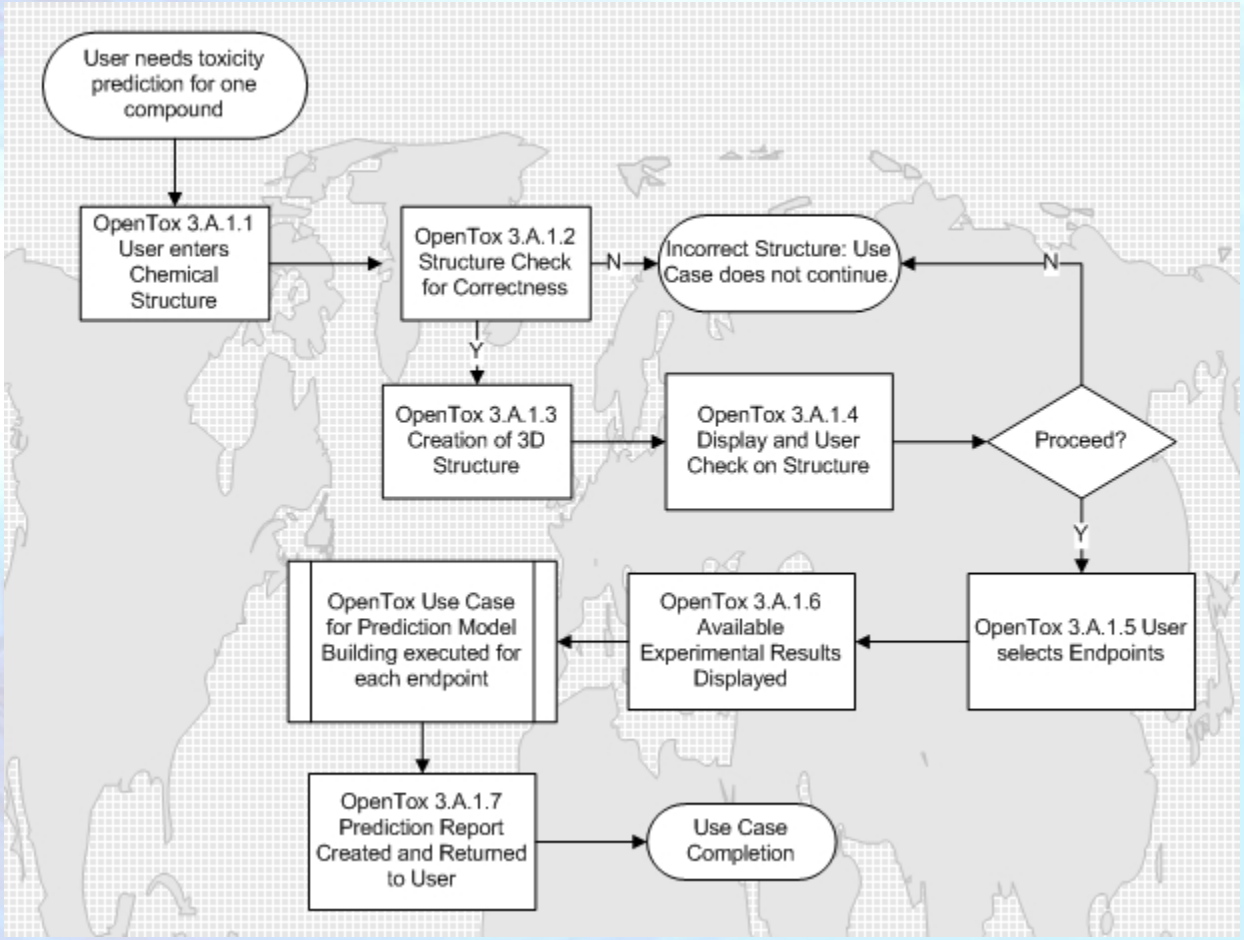
If experimental results for the molecule are found in the database, then the following is printed "Experimental data for this structure is available in the OpenTox database and is summarized here:"

All necessary descriptors are calculated, results of regression obtained, and chemical similarity to calibration molecules evaluated.

The prediction report is provided including the details of the basis for model prediction and including statistical reporting on the reliability of the prediction

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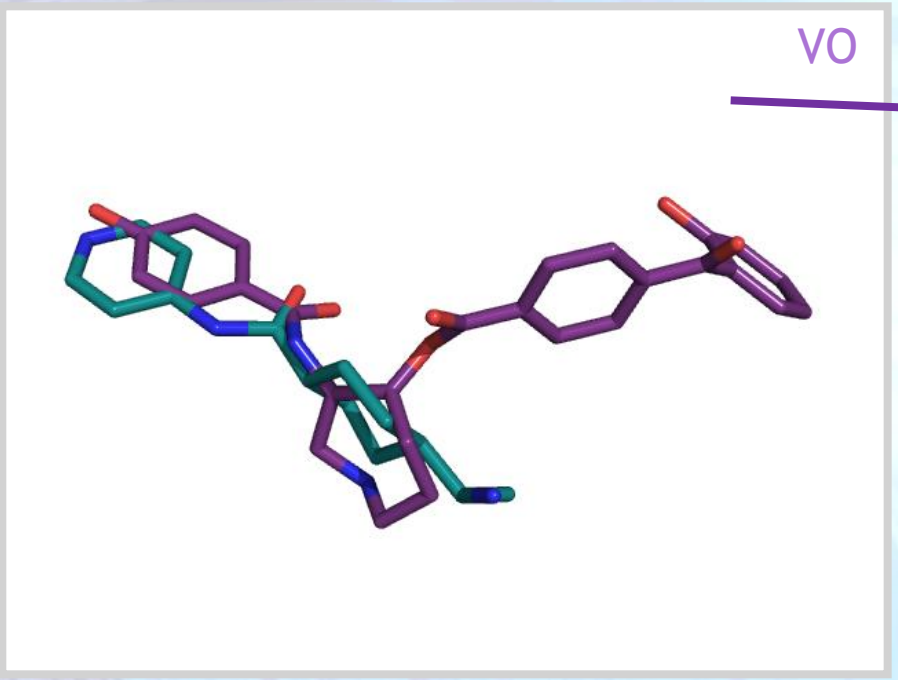
# OpenTox Use Case – given a structure, predict endpoints




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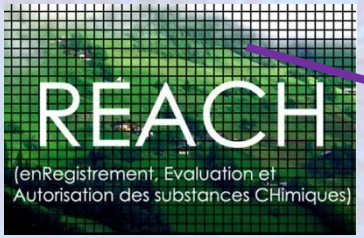
# Pilot Study Specifications – Collaborative Predictive Toxicology Problem

## Input Structure




## Out – Toxic or Not?

- LD50
- Liver Toxicity
- Secondary Metabolites
- Interaction with the hERG Channel?
- Renal Clearance
- Bioavailability
- Mutagenicity
- Carcogenicity
- ReproductiveToxicology
- Skin Irritation
- Aqua Toxicity
- Combined predictions for arrays of mutiple end points




Business Driver

Increasing demands on industry to satisfy safety evaluation and risk assessment required by REACH legislation.

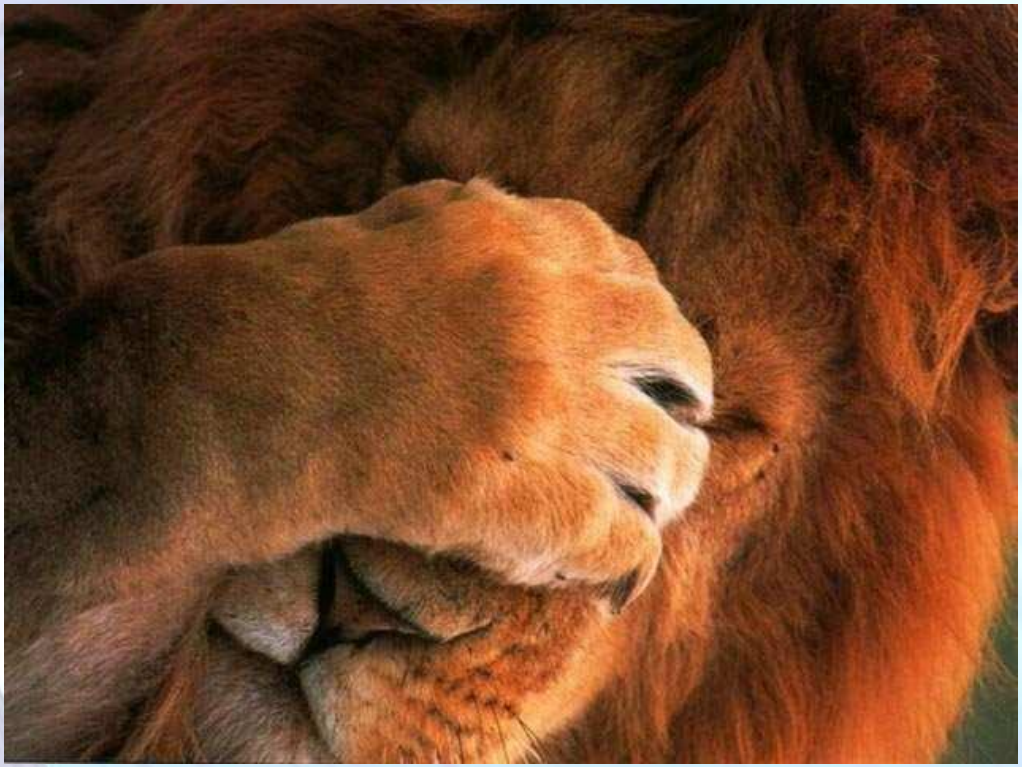
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Our situation today. When we ask..

**Let‘s build an integrated application?**
**Let‘s collaborate on an analysis?**



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**And is it not clear what we need and should do, but...?**

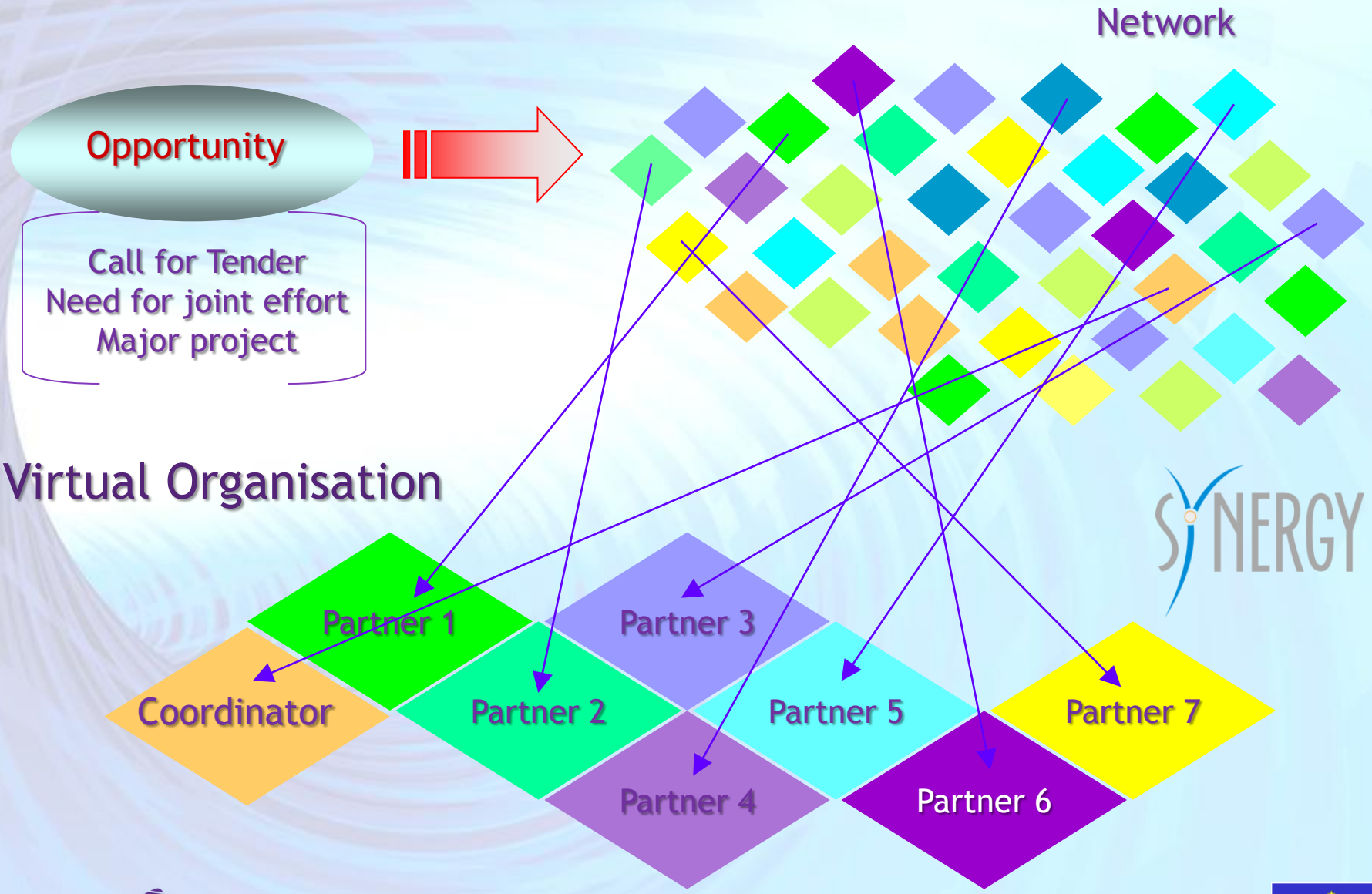
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# And is this how it could be? (at least some of the time ☺)



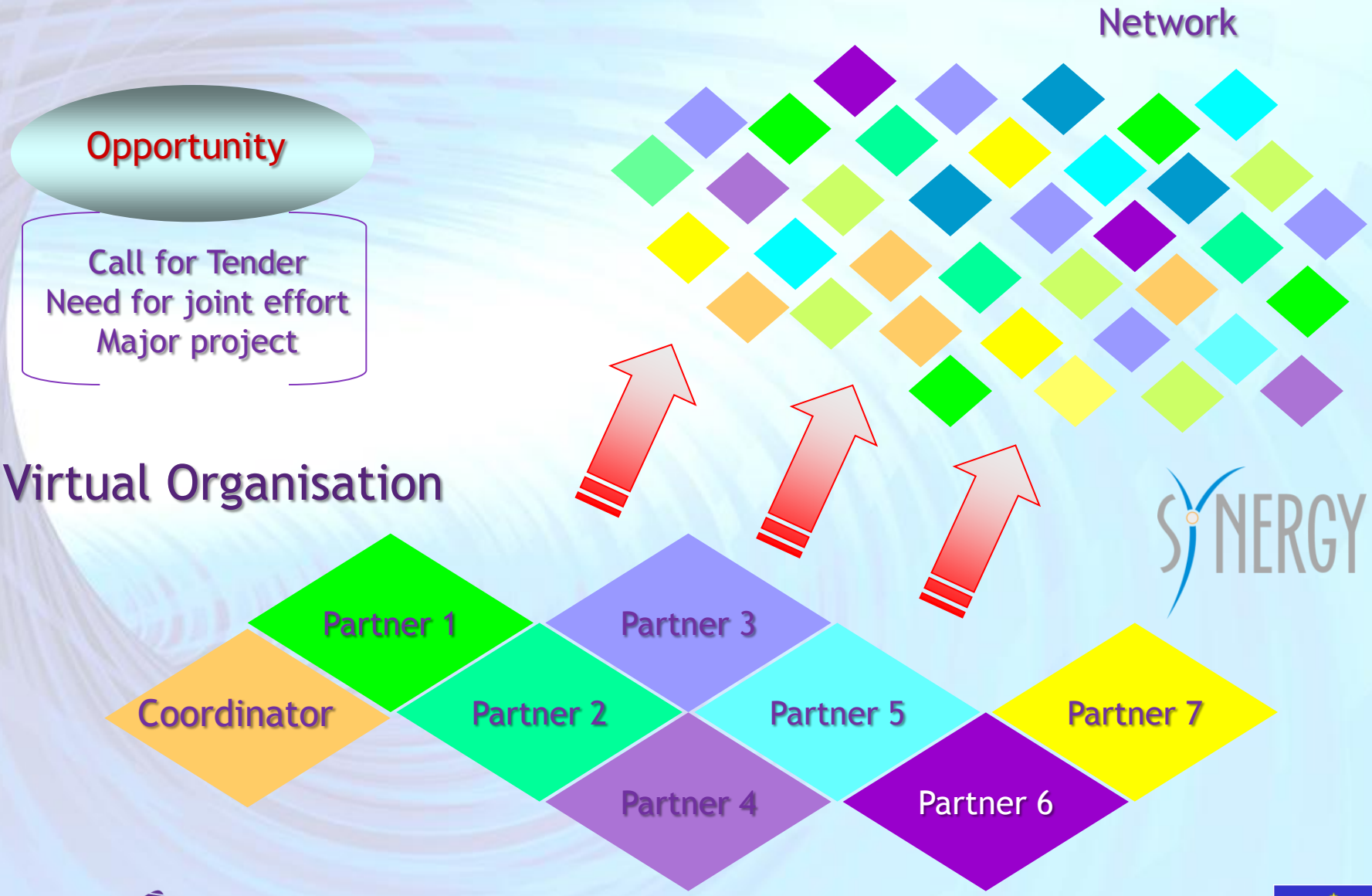
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# Creating Collaborations




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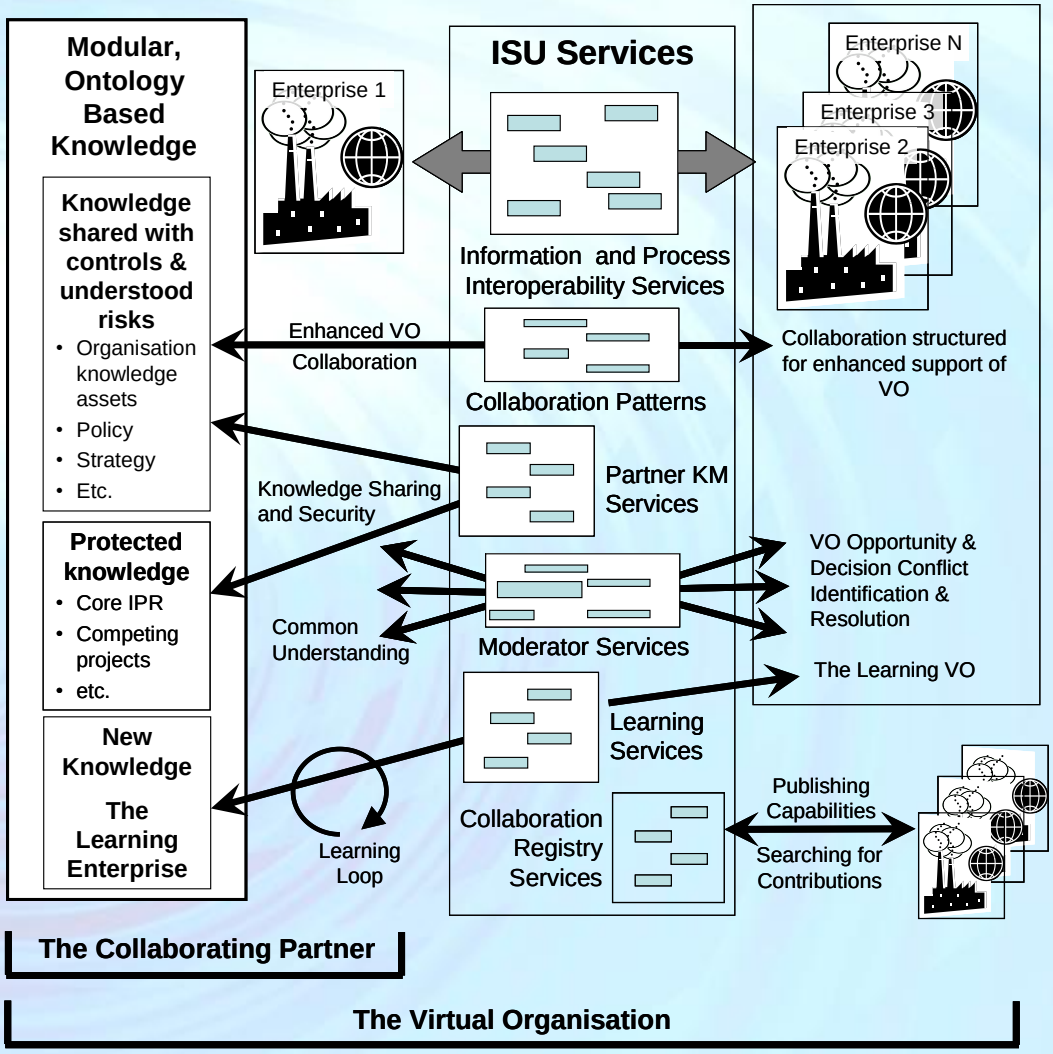
# Creating and Operating Collaborations



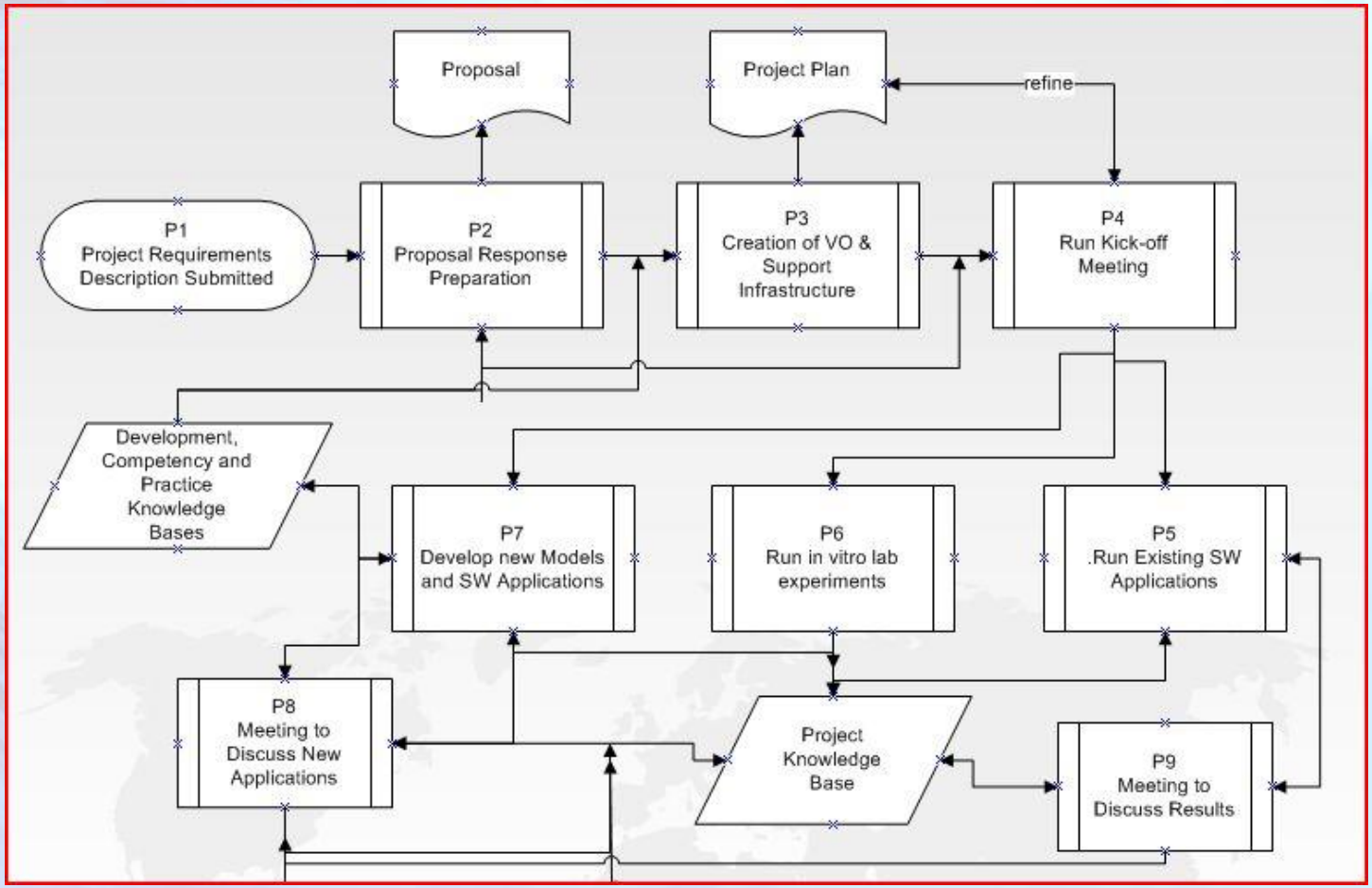

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# Building Collaborations - SYNERGY

SYNERGY website:
http://www.synergy-ist.eu/

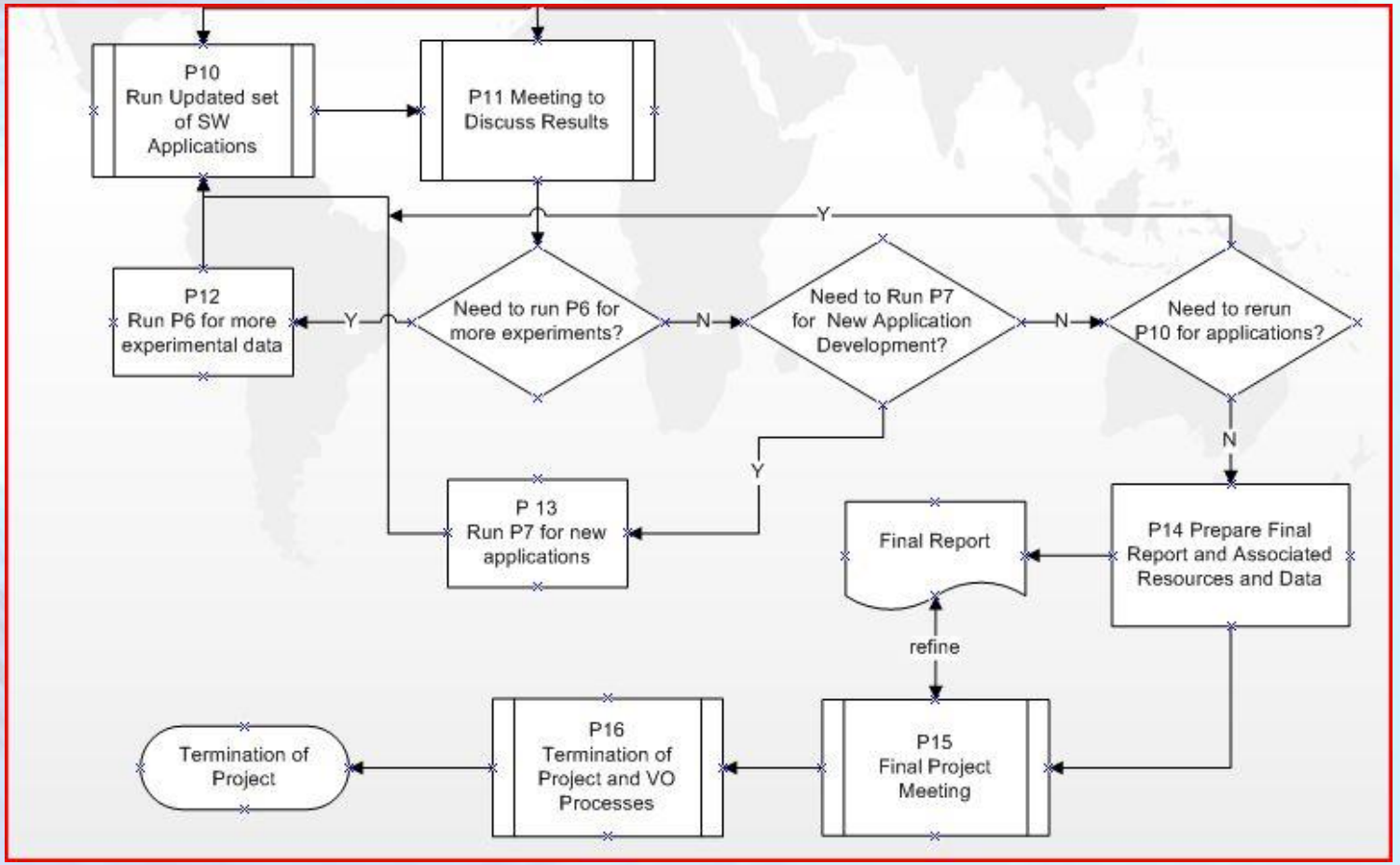


# Collaborative Predictive Toxicology VO Workflow




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# Collaborative Predictive Toxicology VO Workflow




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# Predictive Toxicology VO - Next Steps

- Planning in preparation for initial VO pilot activity starting mid-Spring 2010
- Discussions with community members, partners, service providers etc.
- Address IP issues, Information Rights Management
- Setup of Support Infrastructure and Knowledge Services
- Proposal: Collaborative Toxicology Ontology Workshop *(including federated/foundry approaches and neighbour ontology initiatives)* Timing : Mid- Late Spring 2010

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# Community & Collaboration - CADASTER

## CADASTER

- **'Sister' FP7 project funded under Environment Program**
- to provide practical guidance to integrated risk assessment by carrying out a full hazard and risk assessment for industrial chemicals
- Decision Support System to accommodate and integrate emerging practices and procedures for alternative non-animal based testing methods

## CADASTER & OpenTox

- working closely so as to promote and develop common practices, standards and procedures in the area of *in silico* based predictive toxicology approaches responding to user requirements in the area of REACH-relevant risk assessment
- collaboration should enable the development of a leading platform supporting the safety evaluation and regulatory compliance needs of industry

**More Information at [Cadaster.eu](Cadaster.eu)**

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# Community & Collaboration - ToxCast

OpenTox partners are progressing QSAR model development through international collaboration and participation in evaluating and testing models against toxicological data produced from the US EPA's ToxCast program.

Such models offer the promise of developing the capability of predicting *in vivo* toxicology endpoints based on a combination of *in vitro* data and *in silico* modeling, which would enable the goals of prioritisation and reduced animal testing in addition to improving understanding on mechanism of action (if we can innovate and develop the approaches in coming years!).

**More information on Recent ToxCast Data Summit Proceedings on US EPA site**

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# Prediction of ToxRefDb *in vivo* data with existing models (including lazar and Toxtree)

- Toxtree::Benigni / Bossa rulebase (for mutagenicity and carcinogenicity) confusion matrix
  - The Benigni / Bossa rulebase for mutagenicity and carcinogenicity – a module of Toxtree", by R. Benigni, C. Bossa, N. Jeliazkova, T. Netzeva, and A. Worth. European Commission report EUR 23241 EN

| No alerts for carcinogenic activity | CHR_Mouse_Tumorigen | Count |
|---|---|---|
| NO | Active | 35 |
| YES | Active | 60 |
| NO | Inactive | 64 |
| YES | Inactive | 87 |

correct predictions in green

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# Prediction of ToxRefDb *in vivo* data with existing models (including lazar and Toxtree)

- Toxtree::Benigni / Bossa rulebase (for mutagenicity and carcinogenicity) confusion matrix
  - The Benigni / Bossa rulebase for mutagenicity and carcinogenicity – a module of Toxtree", by R. Benigni, C. Bossa, N. Jeliazkova, T. Netzeva, and A. Worth. European Commission report EUR 23241 EN

| Structural Alert for genotoxic carcinogenicity | CHR_Mouse_Tumorigen | Count |
|---|---|---|
| NO | Active | 70 |
| YES | Active | 25 |
| NO | Inactive | 100 |
| YES | Inactive | 51 |

correct predictions in green

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# Prediction of ToxRefDb *in vivo* data with existing models (including lazar and Toxtree)

- Toxtree::Benigni / Bossa rulebase (for mutagenicity and carcinogenicity) confusion matrix
  - The Benigni / Bossa rulebase for mutagenicity and carcinogenicity – a module of Toxtree", by R. Benigni, C. Bossa, N. Jeliazkova, T. Netzeva, and A. Worth. European Commission report EUR 23241 EN

| Structural Alert for nongenotoxic carcinogenicity | CHR_Mouse_Tumorigen | Count |
|---|---|---|
| NO | Active | 85 |
| YES | Active | 10 |
| NO | Inactive | 138 |
| YES | Inactive | 13 |

correct predictions in green

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# Prediction of ToxRefDb *in vivo* data with existing models (including lazar and Toxtree)

- Toxtree::Cramer tree (threshold of toxicological concern)
  - Cramer G. M., R. A. Ford, R. L. Hall, Estimation of Toxic Hazard - A Decision Tree Approach, J. Cosmet. Toxicol., Vol.16, pp. 255-276, Pergamon Press, 1978

| Low (Class I) | Intermediate (Class II) | High (Class III) |
|---|---|---|
| 9 | 5 | 305 |

~96% of ToxCast Phase I

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# Prediction of ToxRefDb *in vivo* data with existing models (including lazar and Toxtree)

- Toxtree::Verhaar scheme (toxicity mode of action)
  - Verhaar H.J.M., Van Leeuven C., Hermens J.L.M., Classifying Environmental Pollutants. 1: Structure-Activity Relationships for Prediction of Aquatic Toxicity, Chemosphere, Vol.25, No.4, pp.471-491, 1992.

| Class 1 (narcosis or baseline toxicity) | Class 2 (less inert compounds) | Class 3 (unspecific reactivity) | Class 4 (compounds and groups of compounds acting by a specific mechanism) | Class 5 (Not possible to classify according to these rules) |
|---|---|---|---|---|
| 1 | 5 | 27 | 1 | 284 |

~89% of ToxCast Phase I

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# ToxCast Phase 1 Analysis - Insights (1)

- All machine learning approaches had problems with achieving accuracy/specificity/sensitivity goals with the data
- New methods addressing the complexity of such datasets and its sampling, sparseness, balancing and error issues are needed
- Modellers should have more early and ongoing input into the experimental design of such new *in vitro* based R&D programs
- Selective approaches and insights into which information from the *in vitro* data to select for use and for which endpoint are needed
- We need to develop/apply new QSAR approaches and combine with other modelling methods and practices to handle such datasets (e.g., sys bio, pathways, …)
- We need to handle complex and flexible collaborative workflows on co-working on such problems (has become an OpenTox Use Case)

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# ToxCast Phase 1 Analysis - Insights (2)

- Models need to be optimised differently for prioritisation or regulatory purposes in a different manner to general model optimisation e.g., optimising models to minimise false negatives cf. general error
- Paying attention to biological relevance, mechanism, models etc. is very important; statistical-alone approaches are limited
- We need to consider how we integrate simulation approaches, modelling reactivity, ADME modelling, multiple pathways…
- There are some significant chemobiological issues to consider e.g, significant difference between drug and pesticide chemistries and mechanisms, significant difference between high dose in human effects e.g., of a drug cf. chronic longer term lower dose exposure of an environmental chemical, significant issues between predicting effects in animals and humans to address e.g., we are using *in vitro* to predict animal *in vivo* to predict human *in vivo*

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# ToxCast Phase 1 Analysis - Insights (3)

- we need to consider alternative approaches - human stem cell, tissue, systems biology, combining with metabolomics data etc. and how to better integrate different kinds of evidence into consensus predictions
- important validation issues to be addressed in future (e.g., external test sets in ToxCast phase 2)
- taking and evaluating different strategies is good direction to explore e.g., chemical vs pathways vs hybrid
- we should keep in mind that the current main outcome strategy here is that of prioritization for testing/use of signatures rather than general "*ab initio*" prediction merit. (In this respect ToxCast has some similar shared goals and needs as with REACH use case drivers, as we recently discussed at OpenTox workshop in Rome – see blog posts on OpenTox Blog at www.opentox.org)

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# Final words...

Visit the OpenTox website for more information at OpenTox.org

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Many thanks for your attention!



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