Collaborative Development of Predictive Toxicology Applications

CMTPI 2009 Conference, Istanbul

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SEVENTH FRAMEWORK PROGRAMME

Introduction – Collaboration and Community

From Conservation Project Trip in Caprivi Delta

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OpenTox Advisory Board

- European Centre for the Validation of Alternative Methods
- European Chemicals Bureau
- U.S Environmental Protection Agency
- U.S. Food & Drug Administration
- 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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Presentation Outline

- Introduction
- User Requirements
- The OpenTox Framework
- Ontologies
- Algorithms
- Validation and Reporting
- Community and Collaboration
- Building Collaborations
- Discussion and Conclusions

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Introduction - REACH

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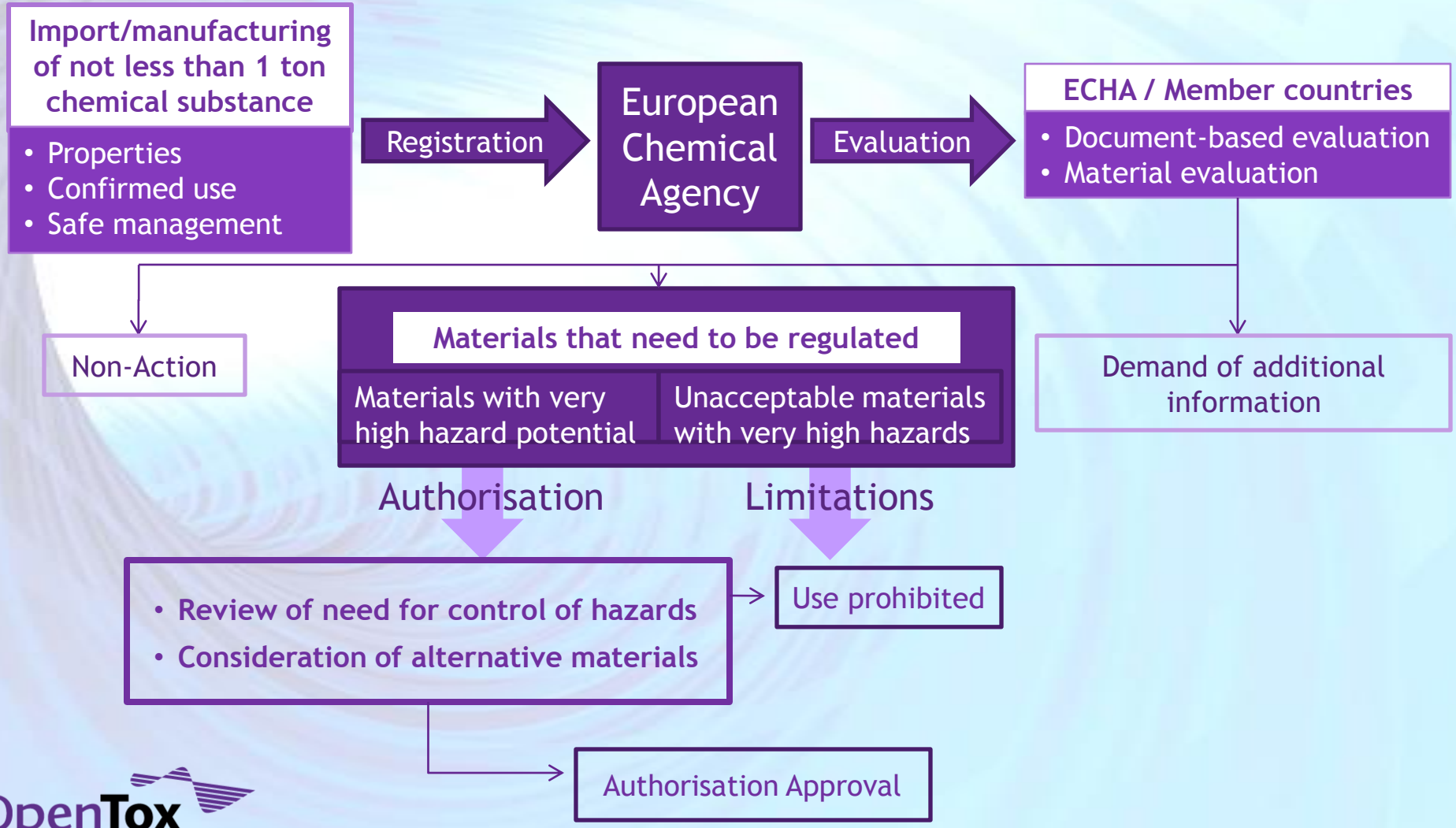
Introduction – REACH registration



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Introduction - 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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Introduction – Goal of reduced animal testing

Visit with Lions at Mukuni Project, Livingstone, Zambia

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Introduction – Taking a look at the Challenges

Visit with Lions at Mukuni Project, Livingstone, Zambia

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Introduction – Challenges to *in silico* Applications

- Toxicity data collected in many different databases using different formats, frequently incompatible with QSAR programs
- Many databases lack important information for QSAR modeling (e.g. chemical structures)
- Hard to integrate confidential in-house data with public data for model building and validation
- QSAR models have been published in a variety of different 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 QSAR tools provide limited support for reliable validation procedures
- Application, interpretation, and development of QSAR models is still difficult for most toxicological experts
- It requires a considerable amount of statistical, cheminformatics and computer science expertise - procedures are labor intensive and prone to human errors

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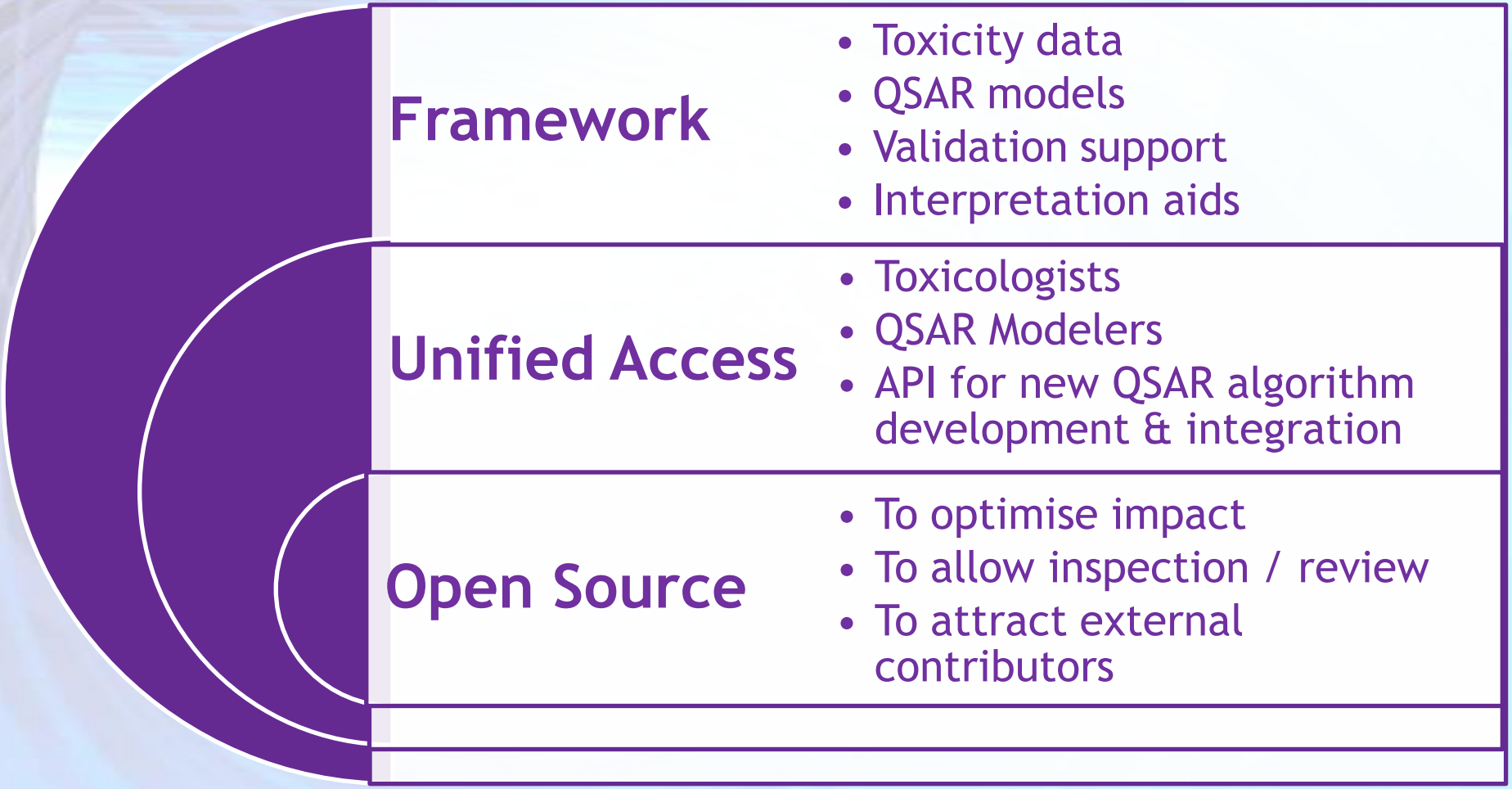
Introduction – OpenTox Goals



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Introduction - About 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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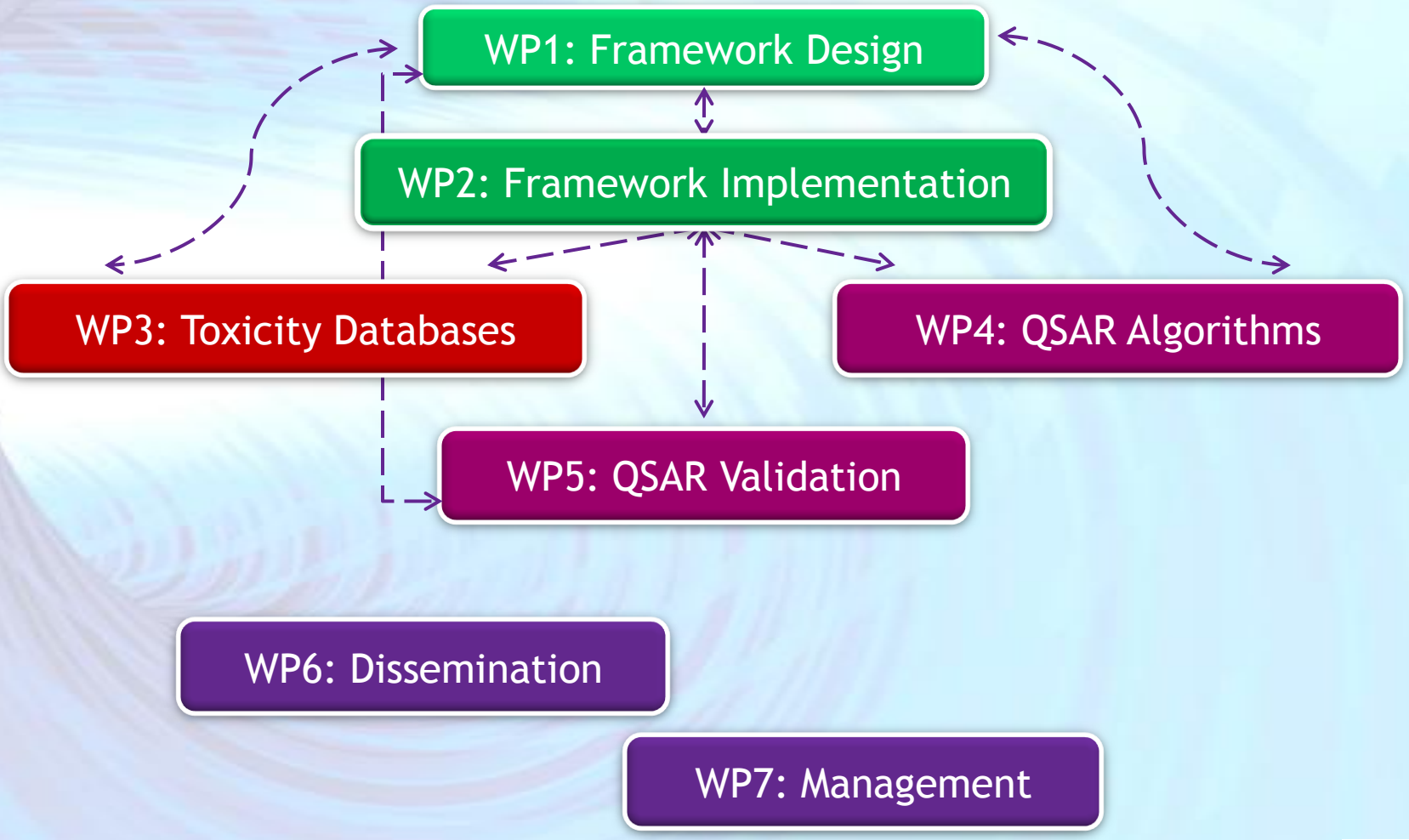
Introduction - OpenTox Work Packages



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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 opentox.org website for evaluation for inclusion in development planning
- 3 hierarchical classes of Use Cases:
  1. **Collaboration / Project Level** eg 3-month development project
  2. **Application Level** eg carry out a REACH-compliant risk assessment for group of chemicals
  3. **Task Level** eg. 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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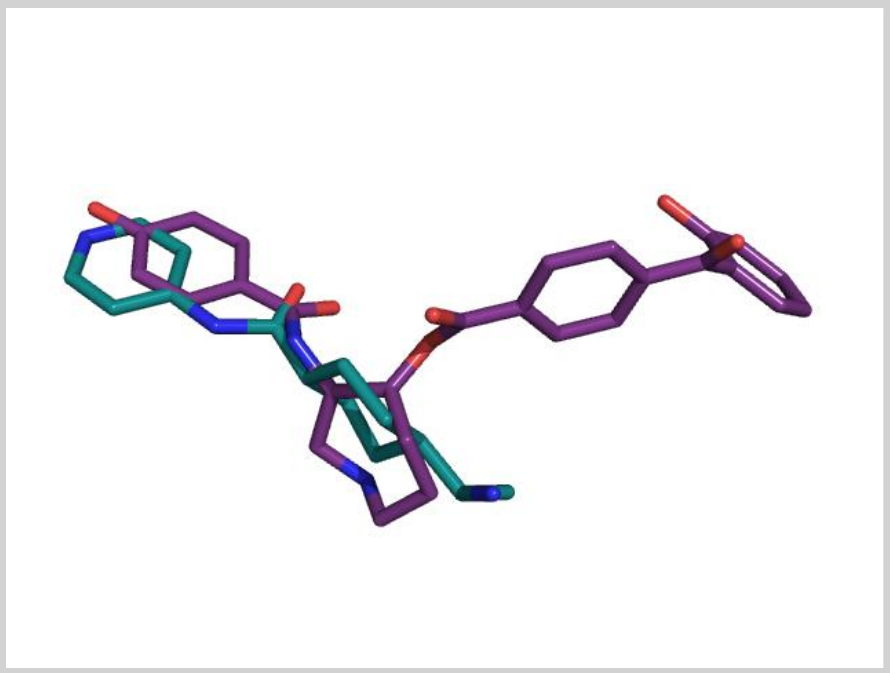
OpenTox Use Case - given a structure, predict endpoints

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
- Virtual Patient Populations

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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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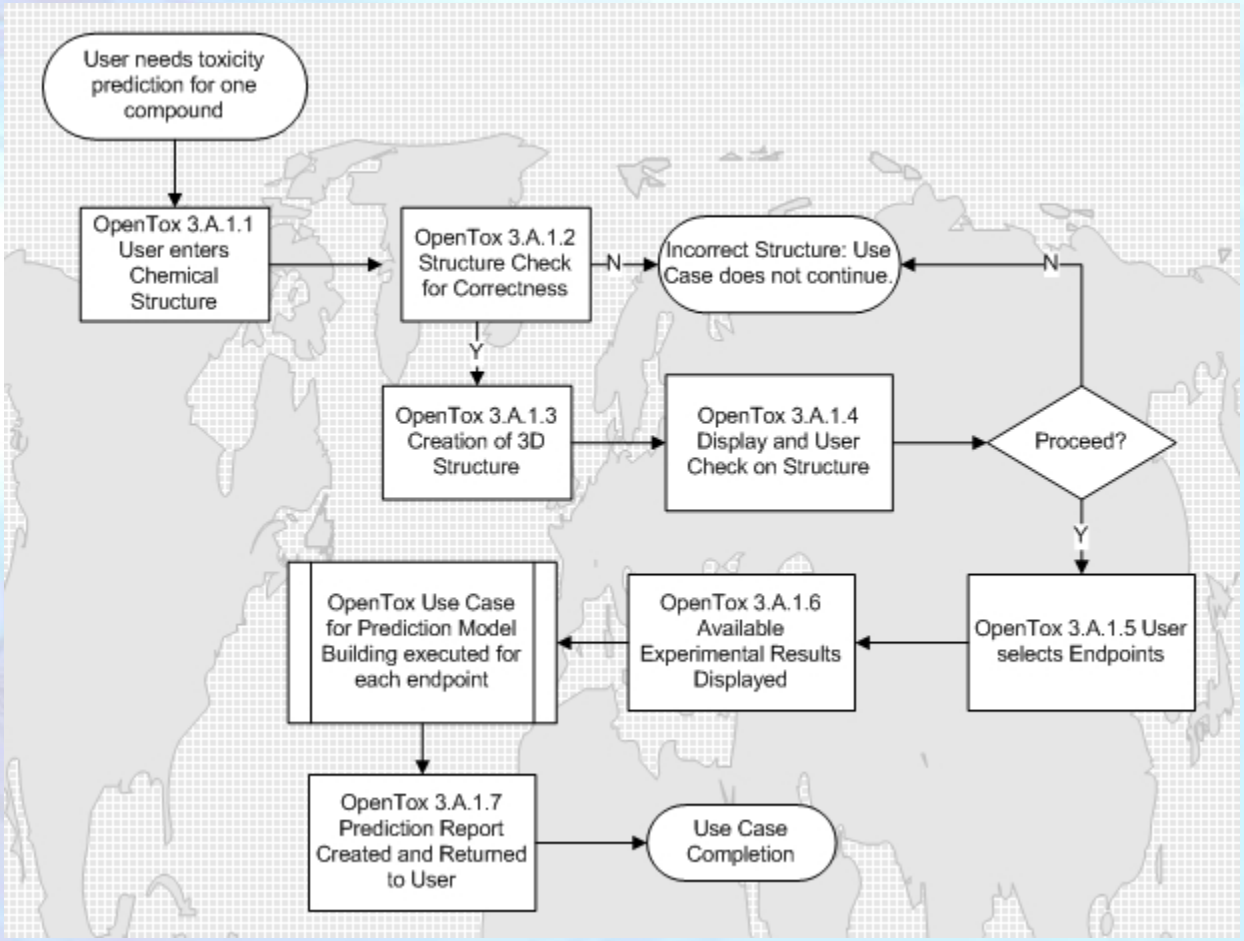
OpenTox Use Case - given a structure, predict endpoints



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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 is an Open Source project
- 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

Current Components

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

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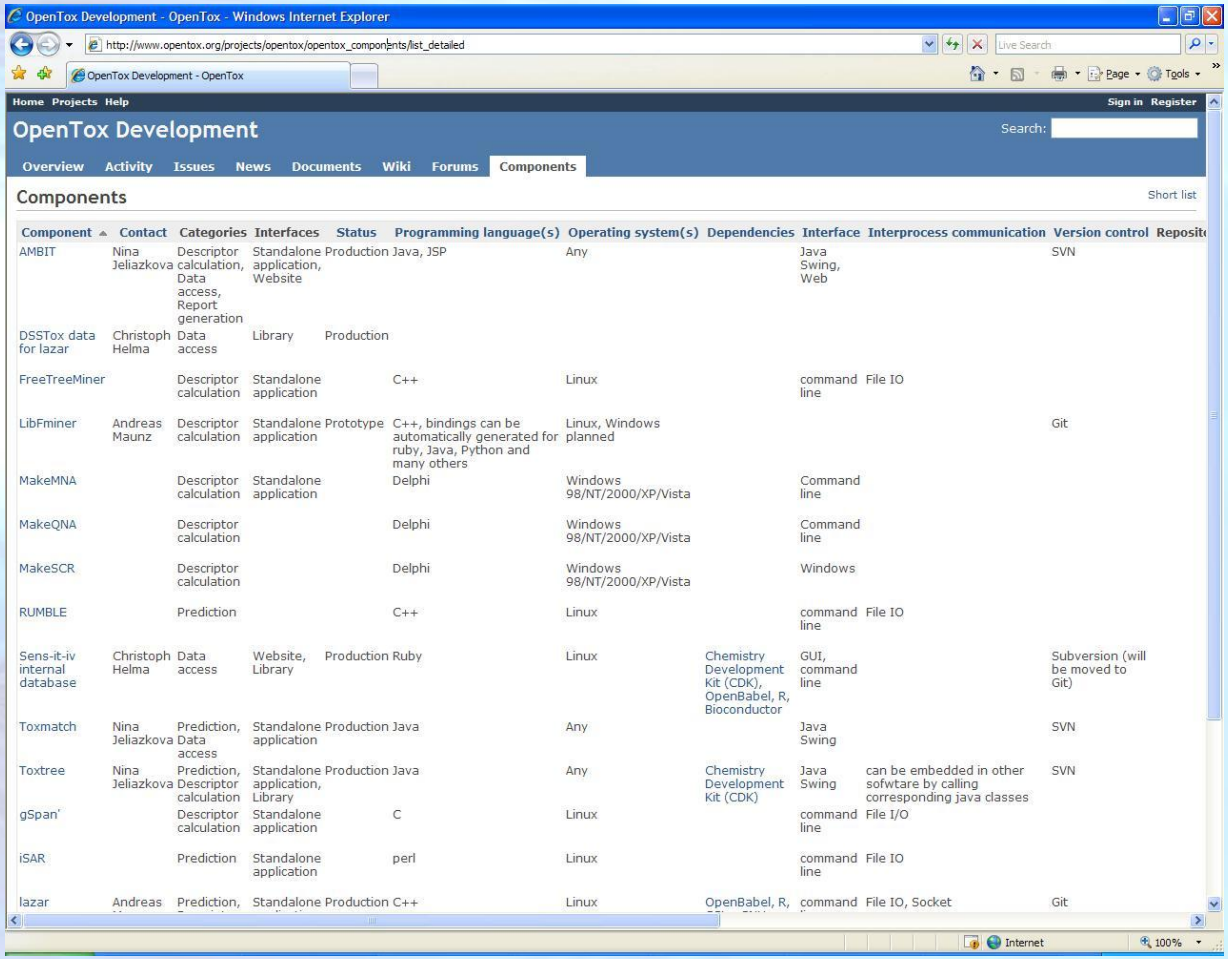
OpenTox Framework - Components



Component	Contact	Categories	Interfaces	Status	Programming language(s)	Operating system(s)	Dependencies	Interface	Interprocess communication	Version control	Reposit
AMBIT	Nina Jeliazkova	Descriptor calculation, Data access, Report generation	Standalone application, Website	Production	Java, JSP	Any		Java Swing, Web		SVN	
DSSTox data for lazar	Christoph Helma	Data access	Library	Production							
FreeTreeMiner		Descriptor calculation	Standalone application		C++	Linux		command line	File IO		
LibFminer	Andreas Maunz	Descriptor calculation	Standalone application	Prototype	C++, bindings can be automatically generated for ruby, Java, Python and many others	Linux, Windows planned				Git	
MakeMNA		Descriptor calculation	Standalone application		Delphi	Windows 98/NT/2000/XP/Vista		Command line			
MakeQNA		Descriptor calculation			Delphi	Windows 98/NT/2000/XP/Vista		Command line			
MakeSCR		Descriptor calculation			Delphi	Windows 98/NT/2000/XP/Vista		Windows			
RUMBLE		Prediction			C++	Linux		command line	File IO		
Sens-it-iv internal database	Christoph Helma	Data access	Website, Library	Production	Ruby	Linux	Chemistry Development Kit (CDK), OpenBabel, R, Bioconductor	GUI, command line		Subversion (will be moved to Git)	
Toxmatch	Nina Jeliazkova	Prediction, Data access	Standalone application	Production	Java	Any		Java Swing		SVN	
Toxtree	Nina Jeliazkova	Prediction, Descriptor calculation	Standalone application, Library	Production	Java	Any	Chemistry Development Kit (CDK)	Java Swing	can be embedded in other sofwtare by calling corresponding java classes	SVN	
gSpan'		Descriptor calculation	Standalone application		C	Linux		command line	File I/O		
iSAR		Prediction	Standalone application		perl	Linux		command line	File IO		
lazar	Andreas	Prediction,	Standalone	Production	C++	Linux	OpenBabel, R,	command	File IO, Socket	Git	

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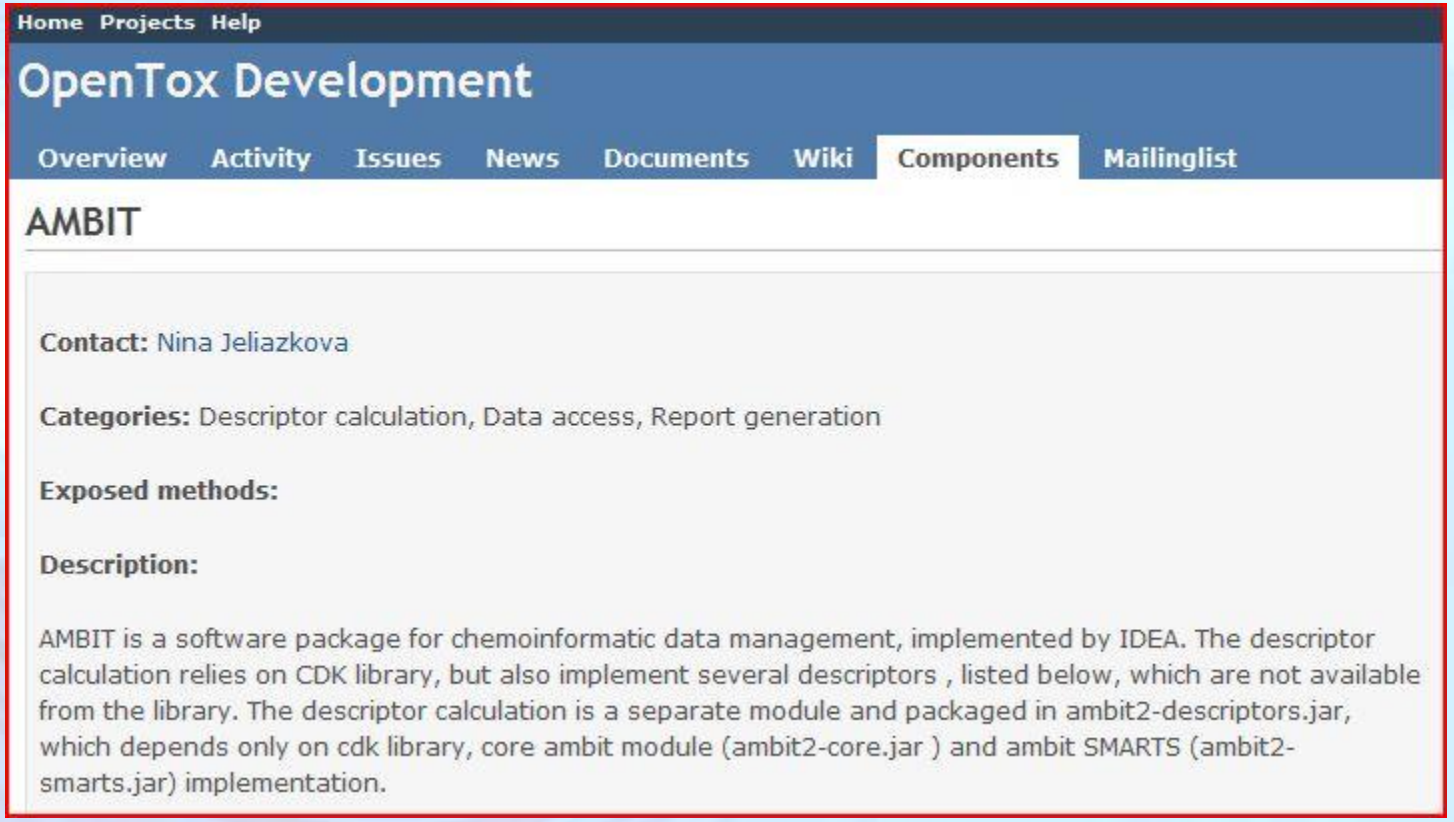
More Information at Opentox.org

OpenTox Framework - Components



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More Information at Opentox.org

OpenTox Framework - Interfaces

The initial specifications for the OpenTox Application Program Interfaces (APIs) have been defined and are being 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

Further tools for the identification of weak points (such as visual inspection of misclassification) will also enable test driven development procedures

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Ontology and Data – Concept and Goals

OpenTox Must	• define the ontology & controlled vocabulary • standardize and organize high-level concepts, chemical information and toxicological data
Needs	• distributed services exchanging communications • 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 • 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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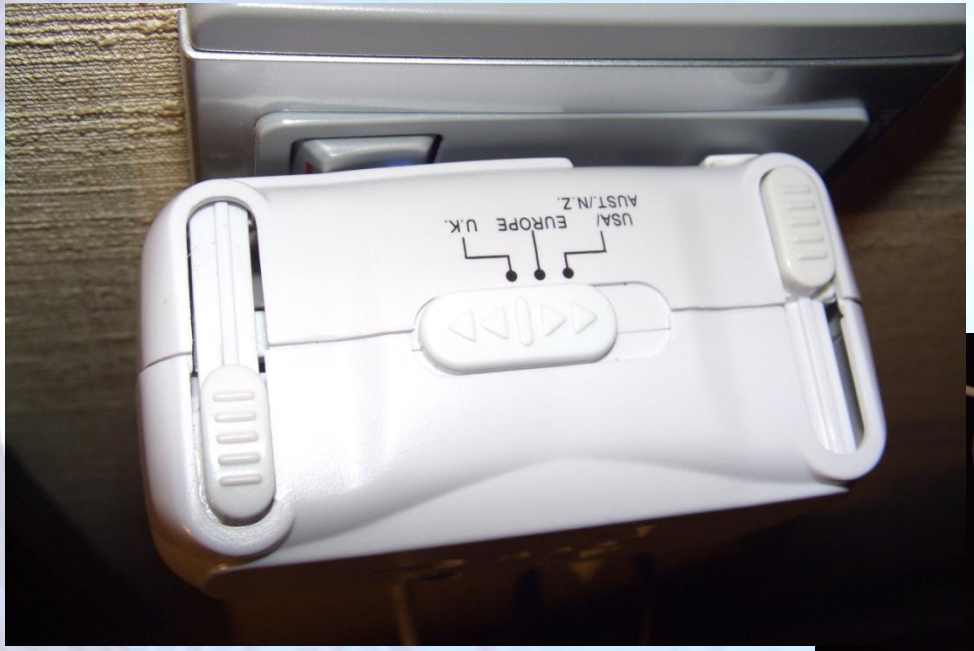
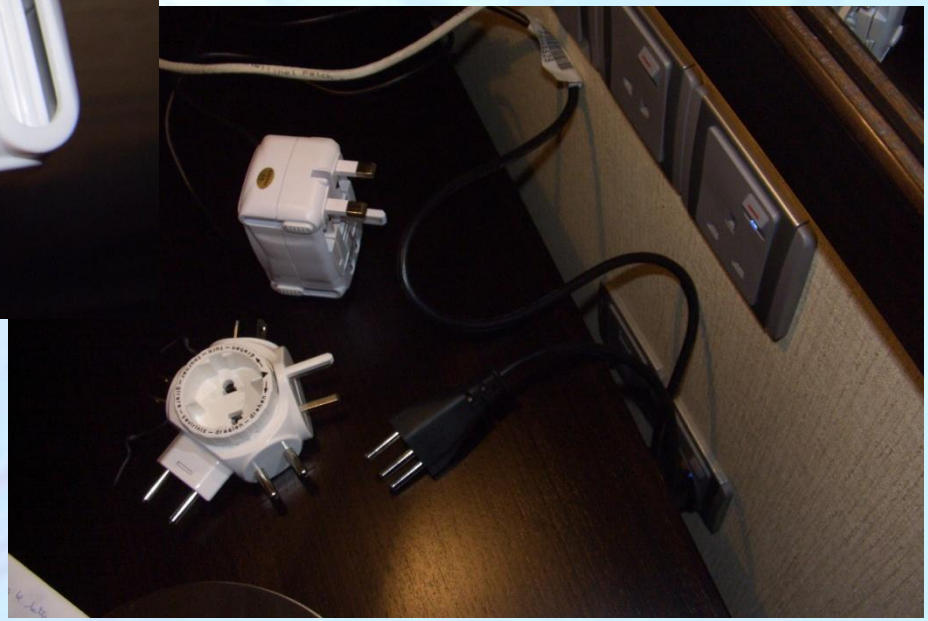
Ontology and Data - Evaluation Conclusion

- 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.

Ontology and Data - Interoperability





Adaptor Challenge in Jeddah, 2008

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Ontology and Data - Interoperability

Adaptor Solution in Jeddah, 2008

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Ontology and Data - Interoperability

Adaptor Solutions in Istanbul, CMTPI 2009

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Algorithms

- OpenTox provides the algorithms that derive data-based predictions and models
- Predictions are visualized by the framework's GUI or serve as input for validation routines
- The open architecture is designed to allow an easy integration of external programs (open source and commercial)
- A flexible plug-in architecture for applying, testing and validating algorithms interactively and systematically is used
- OpenTox is starting with the integration of chemoinformatics, statistical and data mining tools including functionality from other open source projects (e.g. R, WEKA, KNIME, CDK, OpenBabel)
- OpenTox algorithms offer support for common tasks, such as feature generation and selection, aggregation, and visualization

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Algorithms - type and selection

- Selection criteria for algorithm selection in the OpenTox framework development were established
- Algorithm Categories
  - descriptor calculation algorithms
  - classification and regression algorithms
  - feature selection algorithms
- Algorithm Templates Created and Completed – see OpenTox website for documentation
- Algorithm developers in the community may submit further algorithms for potential inclusion in the framework and development planning using the template format

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Algorithms - Template Fields

- Input, Output, Input format and Output format
- User-specified Parameters and Reporting information
- Background
- Type of Descriptor
- Applicability Domain/Confidence in Prediction
- Bias, lazy/eager learning and Interpretability of models
- Class-blind/class-sensitive feature selection
- Type of Feature selection and of approach
- Performance
- OpenTox availability, License/Dependencies
- Convenience of Integration and Priority
- Author of Method, Author of description, contacts and comments

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Algorithms - list of inclusions

Toxmatch	Toxtree	iSAR	Lazar
Ambit	FreeTreeMiner	LibFminer	gSpan’
MakeMNA	MakeQNA	MakeSCR	More to come?

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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 (eg. 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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Validation - Use Case for a Prediction Model

1	User input: - Prediction model - Training structures and activities - Testing structures and activities or validation algorithm
2	Create test sets with validation algorithm (if no test structures are provided)
3	Remove overlapping compounds between training and test sets
4	Create prediction model with training set
5	Predict test set with prediction model
6	Repeat n-times for n-fold Cross Validation
7	Display summary statistics

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OpenTox Reporting Types

Prediction of a single (unseen) component	*Activity, applicability domain, confidence*
Prediction of a range of (unseen) component	*Ranking according to activity / confidence*
Validation of a model	*Different performance criteria (on various datasets), based on cross-validation / external test set validation*
Making predictions on a particular dataset	*Prediction results of various algorithms*
Comparison of different models/algorithms	*Ranking according to different performance criteria*
Evaluation of a feature generation algorithm	*Performance of various algorithms using the generated features compared to other features*
Evaluation of a feature selection algorithm	*Performance of various algorithms using the selected features compared to no feature selection*

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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

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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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Andreas Maunz[1], Christoph Helma[1,2], and Stefan Kramer[3]:

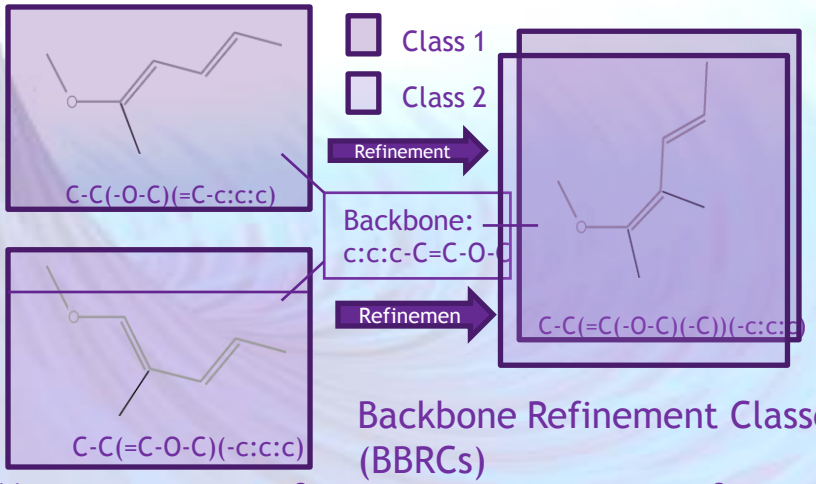
Large-Scale Graph Mining using Backbone Refinement Classes

In KDD '09: Proceedings of the 15th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining.

Mining structurally diverse 2D-descriptors from large class-labelled graph databases.

Specialize on tree-shaped fragments

- Efficient to mine.
- Considers branched substructures.
- **Method: Backbone Refinements** partition the search space **structurally** in contrast to open/closed fragments.



Backbone Refinement Classes (BBRCs)

Mine most significant representative for every class (**BBRC-Representatives**).

BBRC-Representatives:

- Significantly improve accuracy in classification tasks compared to open/ closed fragments.
  - *Sensitivity >75% for carcinogenicity*
- Drastically reduce feature set sizes and running times (dynamic vs. static upper bound pruning).
  - *23,400 compounds in <5min, yielding 31,450 descriptors.*
- yield high descriptor coverage despite high min. frequencies.

C++ library implementation:
www.maunz.de/libfminer-doc

1) FDM Universität Freiburg (D)
2) in-silico toxicology Basel (CH)
3) Technische Universität München (D)

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Prediction of ToxRefDb *in vivo* endpoints with existing models (lazar, PASS, Toxtree…)

- Many of the existing models perform poorly when predicting ToxRefDb *in vivo* endpoints, eg. in terms of false negatives and CPDB-based model predictions, even within their applicability domain
- There is evidence that new models need to be developed, taking into account the chemical classes in ToxRefDb as well as features of the *in vitro* ToxCast data which include challenging unbalanced and sparse data
- ToxRefDb does not currently provide data for some important endpoints such as toxicity mode of action or biodegradibility - it would beneficial if such data could be gathered and provided in the future

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Watch out for those elephants …

From Conservation Project Trip in Caprivi Delta

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And other challenges ahead …

From Conservation Project Trip in Caprivi Delta

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Building Collaborations

opportunity to build collaborative projects on foundation of OpenTox

experiences of having 11 partners collaborate for the ToxCast phase 1 dataset was that a more effective & structured approach to future collaborative projects required

a workflow with process step templates, for a group working on a collaborative predictive toxicology project using a Virtual Organisation (VO) structure

processes are documented from the business, scientific, and knowledge point of view of end users and their individual and collective work process needs

such a collaboration is knowledge-intensive and potentially involving unexpected events, conceptual or technical challenges arising and analysis complexities

it is expected that event-driven *ad hoc* adjustments or dynamic changes to the workflow may be required during its execution

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Building Collaborations – structuring the chaos!

From Conservation Project Trip in Caprivi Delta

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Building Collaborations – structuring the chaos!

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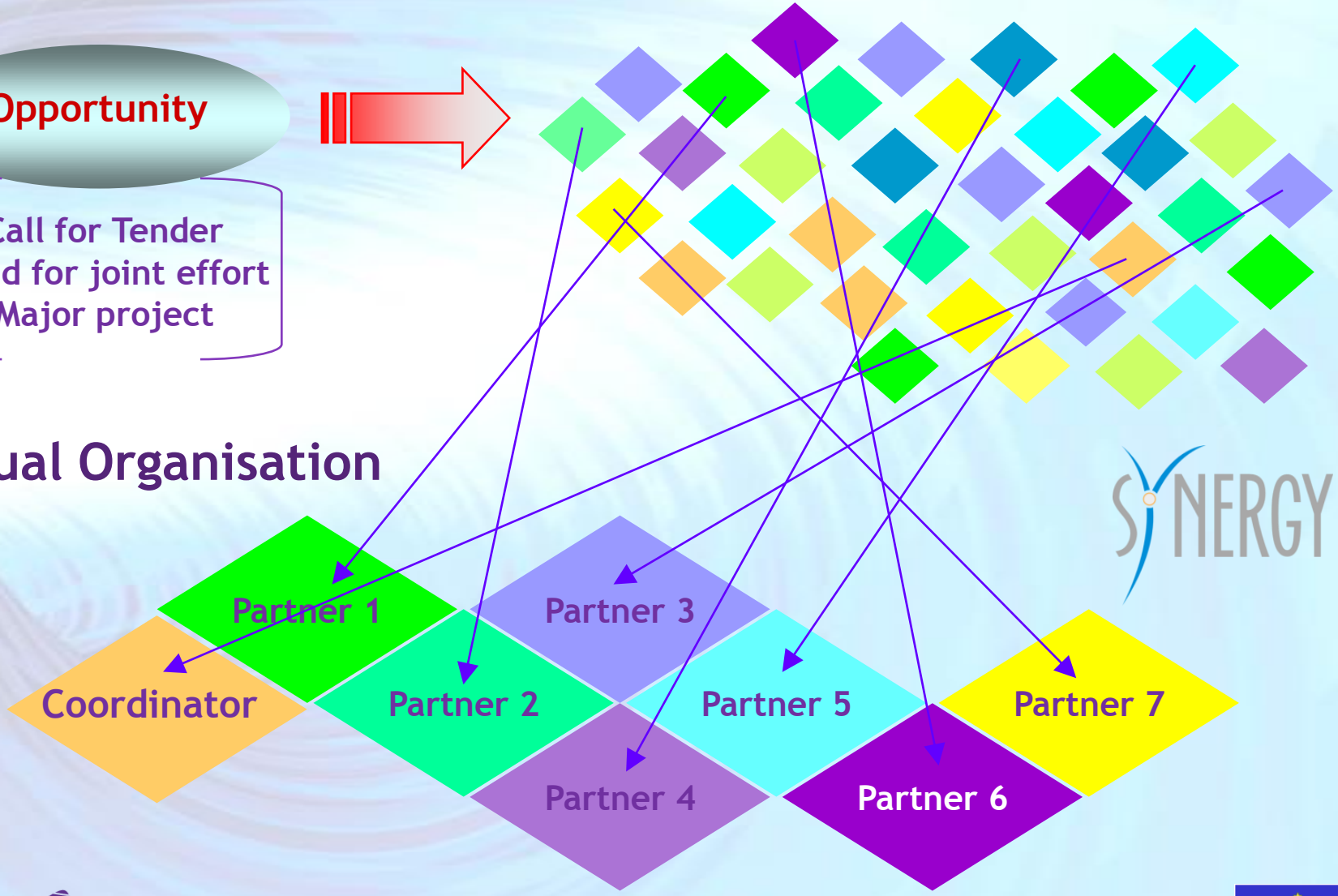
Building Collaborations – Virtual Organisation

Opportunity

Call for Tender
Need for joint effort
Major project



SYNERGY

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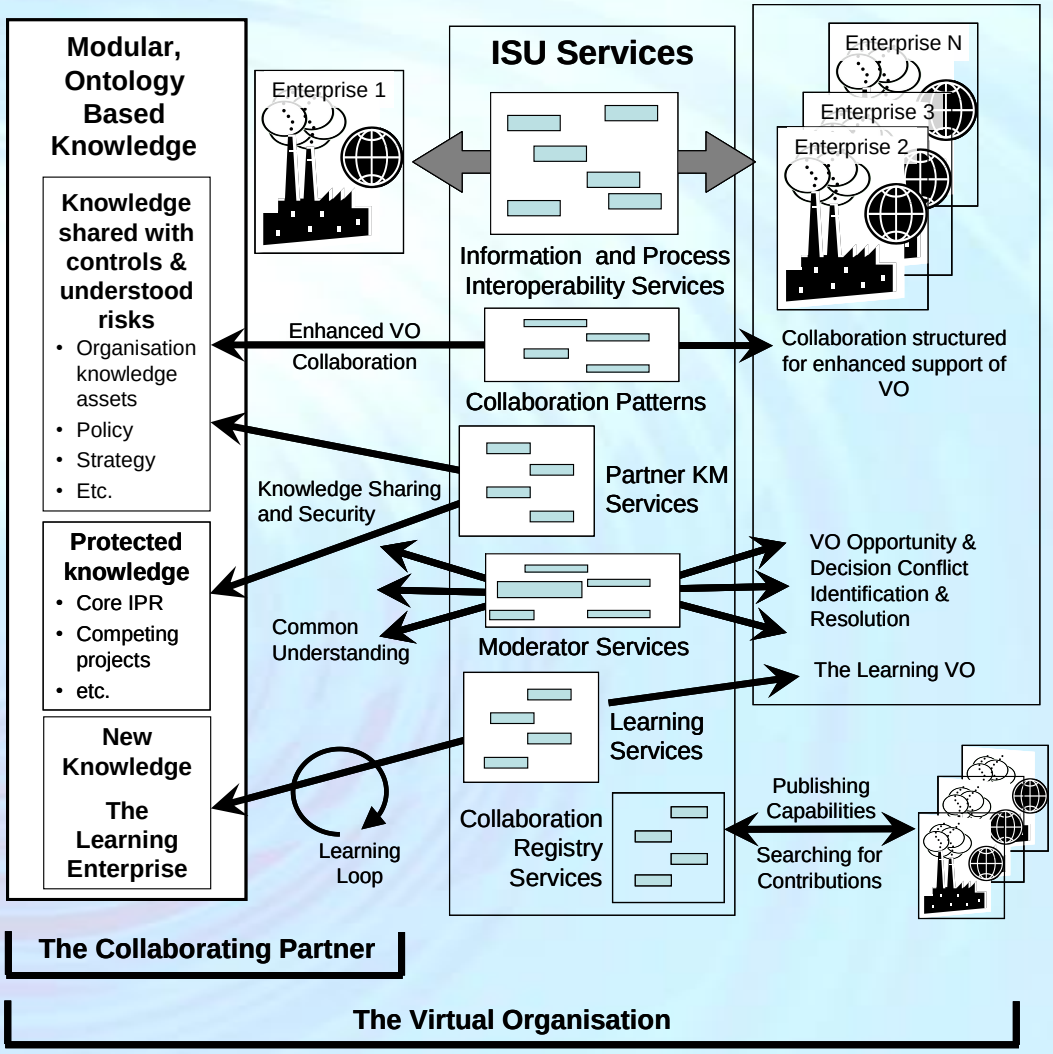
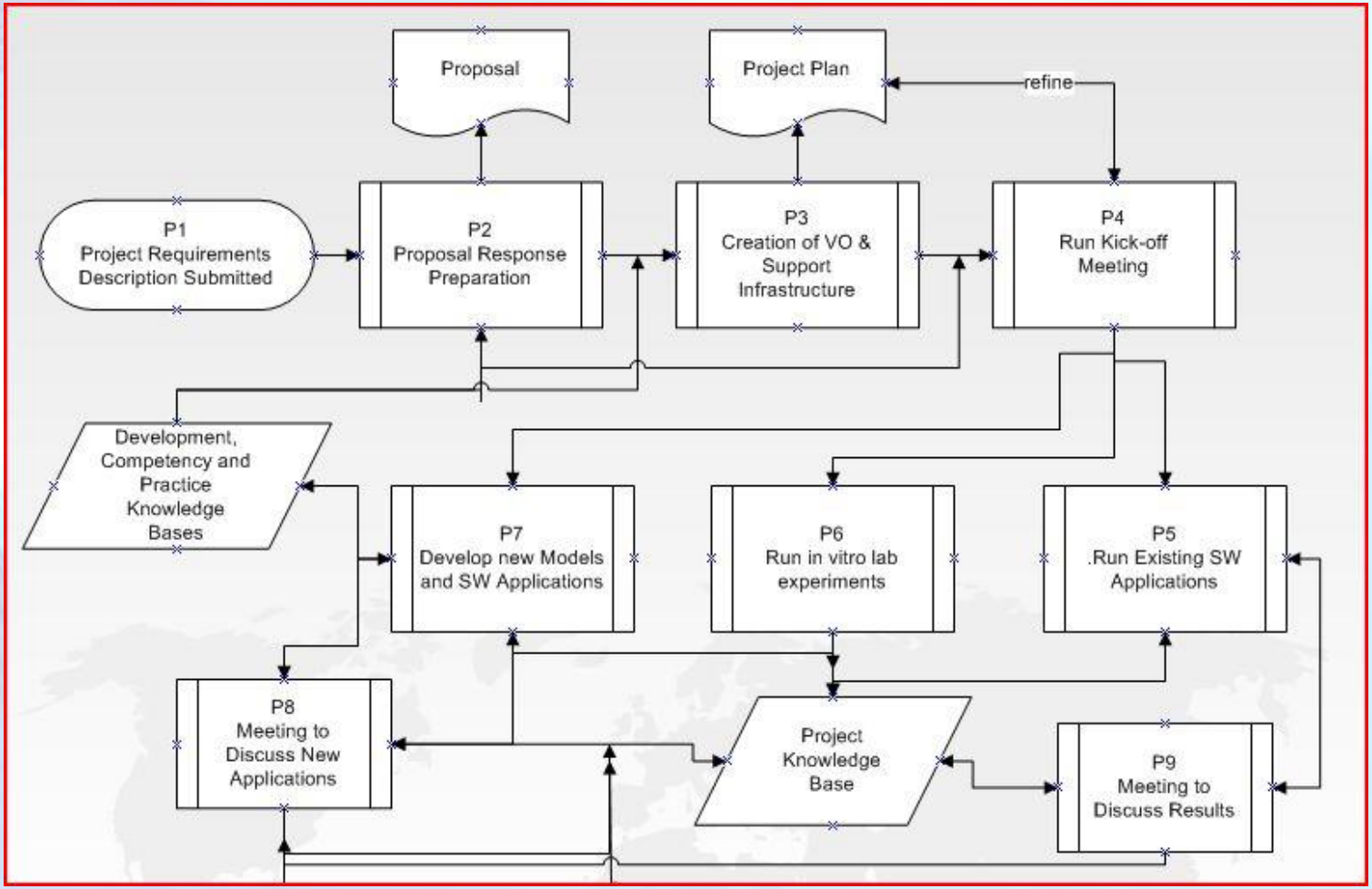
Building Collaborations - SYNERGY

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



Collaborative Predictive Toxicology Workflow



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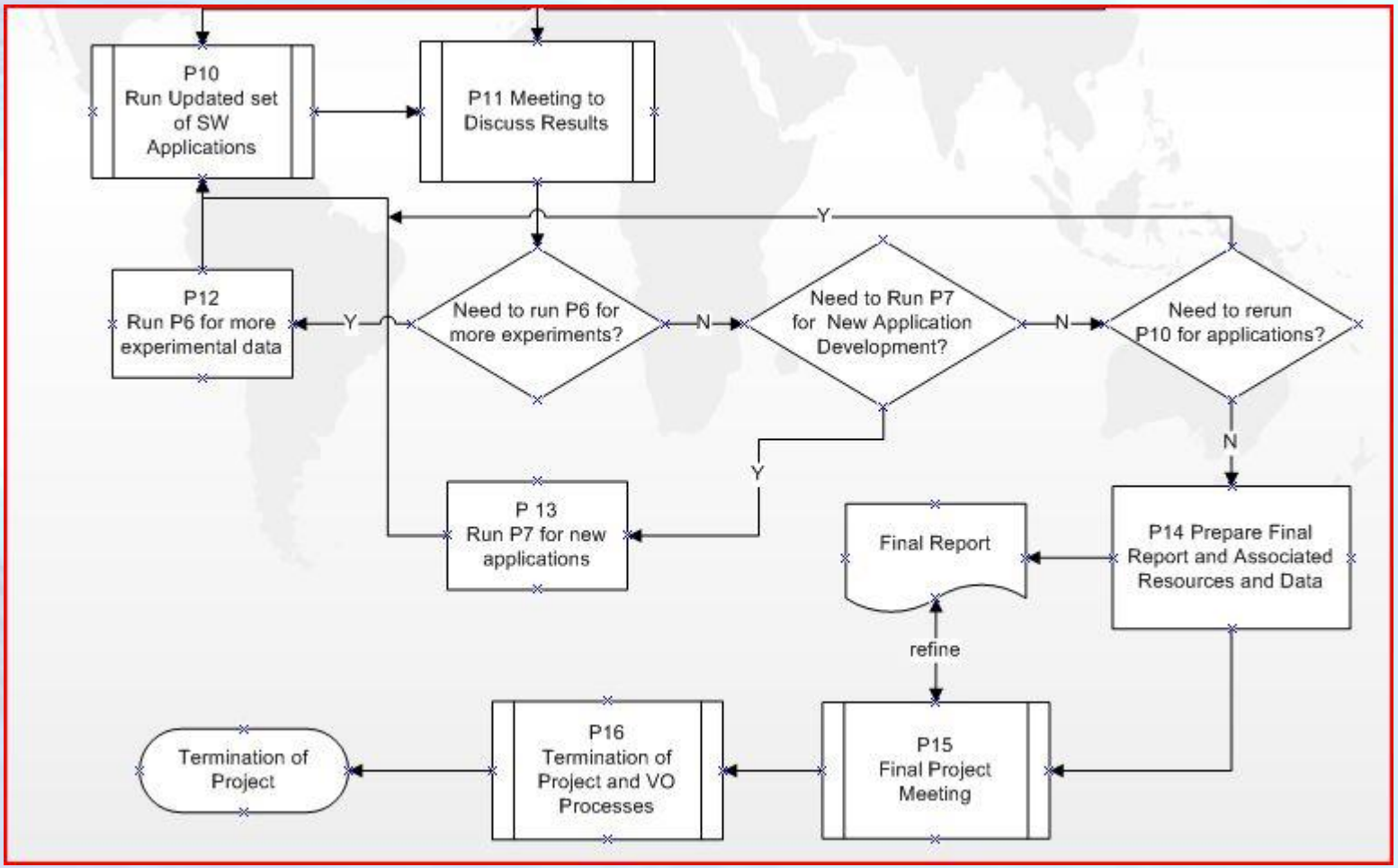
Collaborative Predictive Toxicology Workflow



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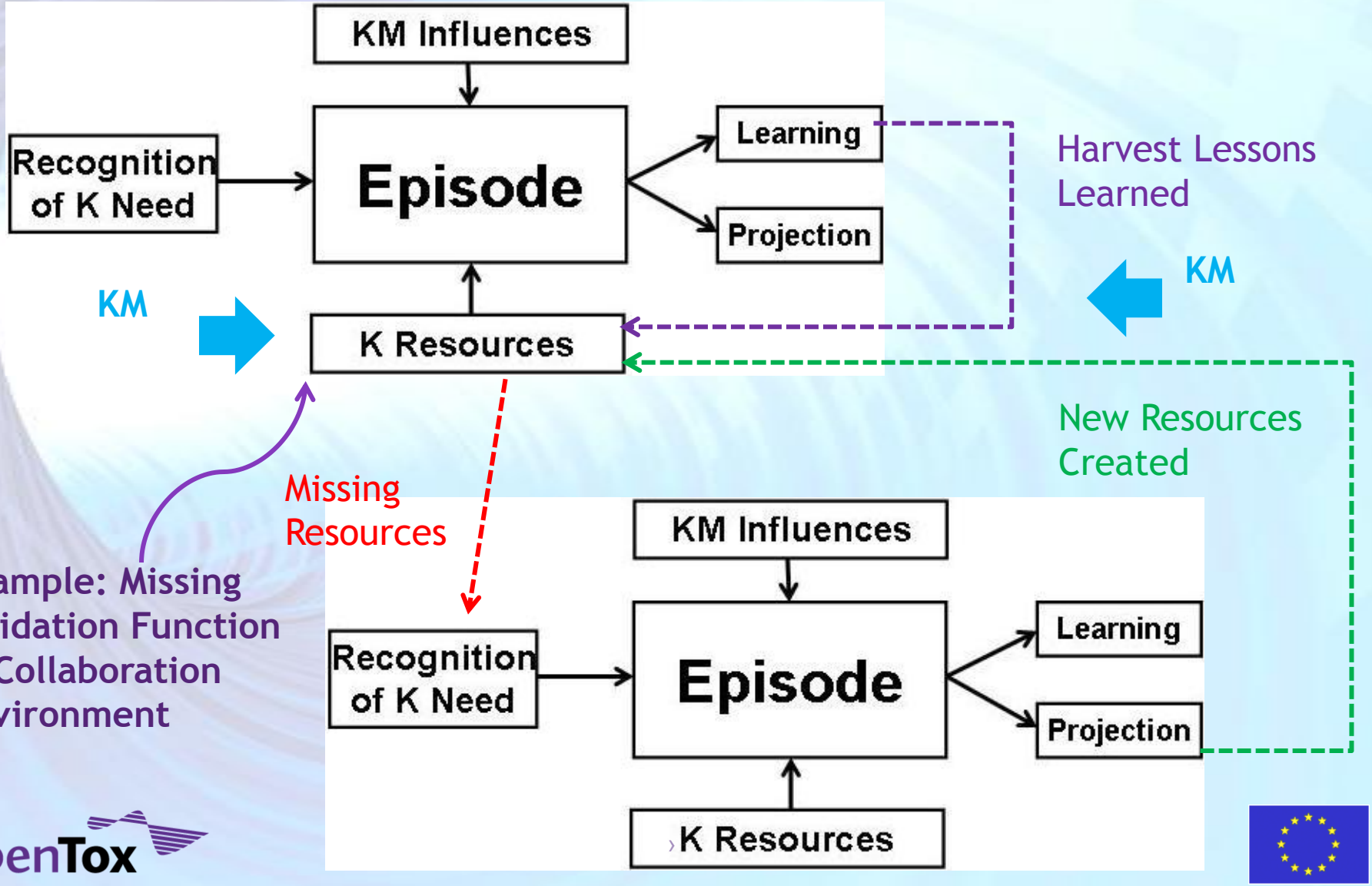
Building Collaborations – Process-oriented Knowledge Management



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Building Collaborations – Knowledge Sharing

InnovationWell Knowledge Café, Bryn Mawr

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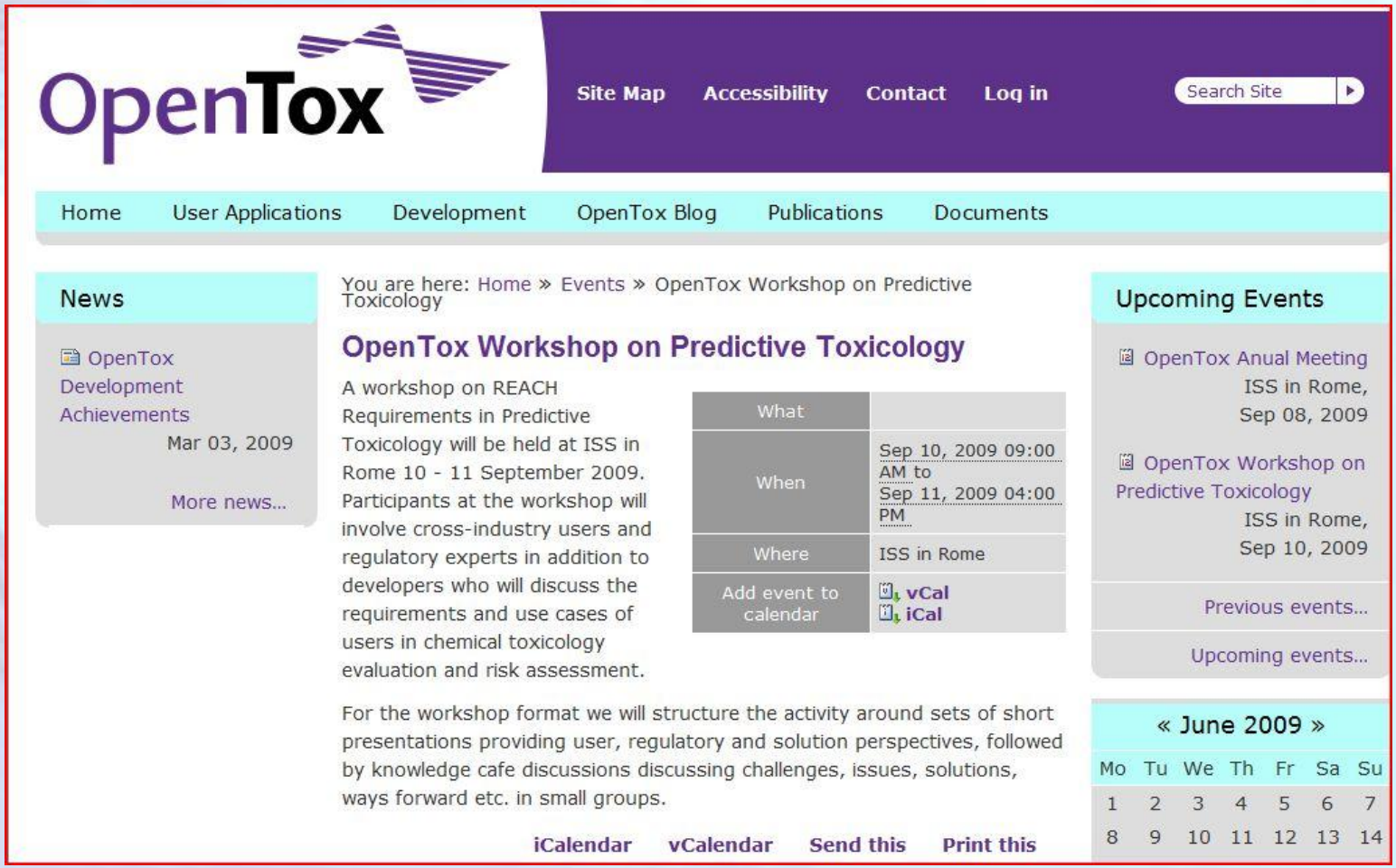
Looking ahead….

From Conservation Project Trip in Caprivi Delta

New OpenTox website with community, content management, and collaboration areas…



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Conclusion - Potential OpenTox Impacts

- improving interoperability
- common standards for data and model exchange)
- increasing the reproducibility of QSAR models
- providing scientifically sound and validation routines
- speed up in development cycle
- inclusion of international community of external developers and researchers
- reduce the costs for candidate development
- reducing the number of expensive efficacy and toxicity animal experiments
- compounds with potential adverse effects will be removed earlier from the product pipeline which saves not only toxicity experiments, but also *in vivo* efficacy experiments.

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Conclusion - Potential OpenTox Impacts on REACH

ECB estimates that the initial implementation of REACH could result in an additional **3.9 million** animals being used

↓

Chronic effects like reproductive and developmental toxicity, *in vivo* mutagenicity & carcinogenicity will require ~72% of the test animals (~2.8 million animals)

↓

QSAR techniques estimated to reduce animal tests by 33-50%

↓

OpenTox focuses initially on improved QSAR techniques for reproductive, developmental and repeated dose toxicity, and for *in vivo* mutagenicity and carcinogenicity endpoints

↓

So OpenTox could play a major role in the reduction of 1.4 million animal experiments alone for REACH!

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Final words...

Visit the OpenTox website for more information at OpenTox.org

Contact me:

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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).