

# Integrated Predictive Toxicology Application Development

EMBL-EBI Industry Program Workshop  
**Toxicogenomics & Toxicoinformatics**  
*23 November 2009, Hinxton, UK*

presented by Barry Hardy  
Douglas Connect  
OpenTox Project Coordinator

# Our Drivers - Collaboration and Community

*So now I have explained our game, how does yours work?*





# Our Drivers - Sustainability and Diversity



[Visit with Lions at Mukuni Project, Livingstone, Zambia](#)



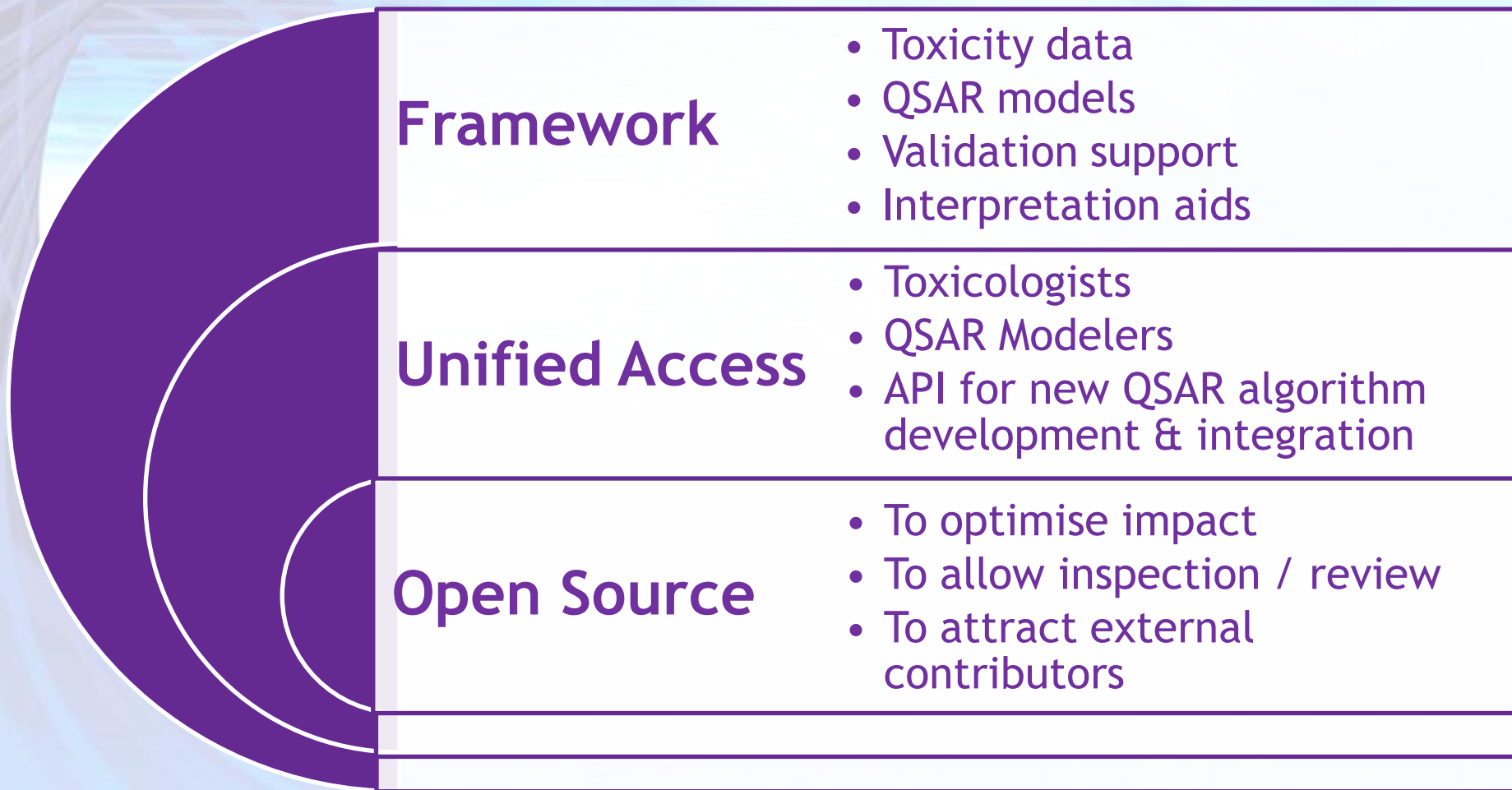
# Our Drivers - Taking on Technical, Cultural and “Other” Challenges of the Unexpected



# 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

# OpenTox Approach

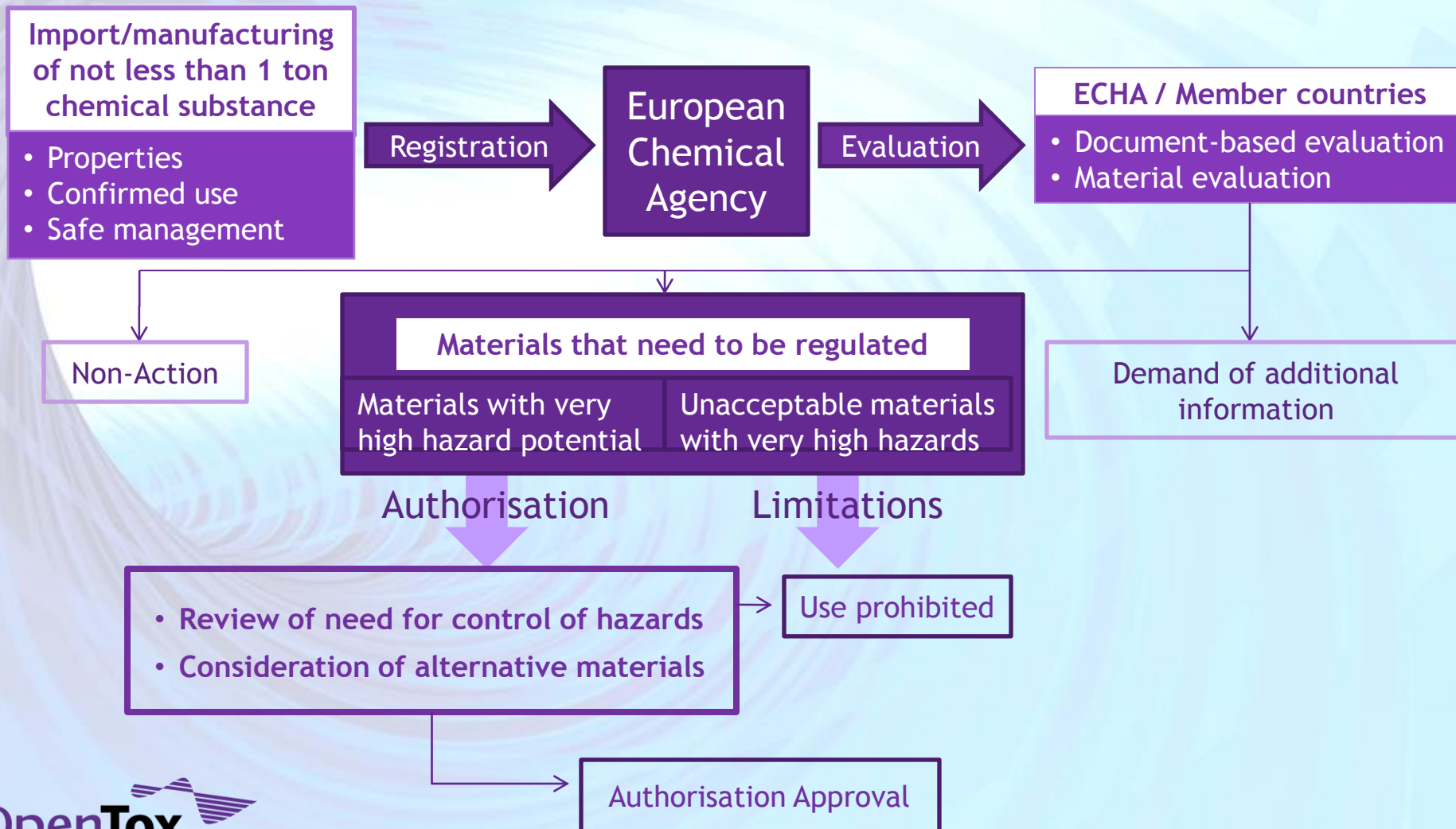




# REACH



# REACH registration





# 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

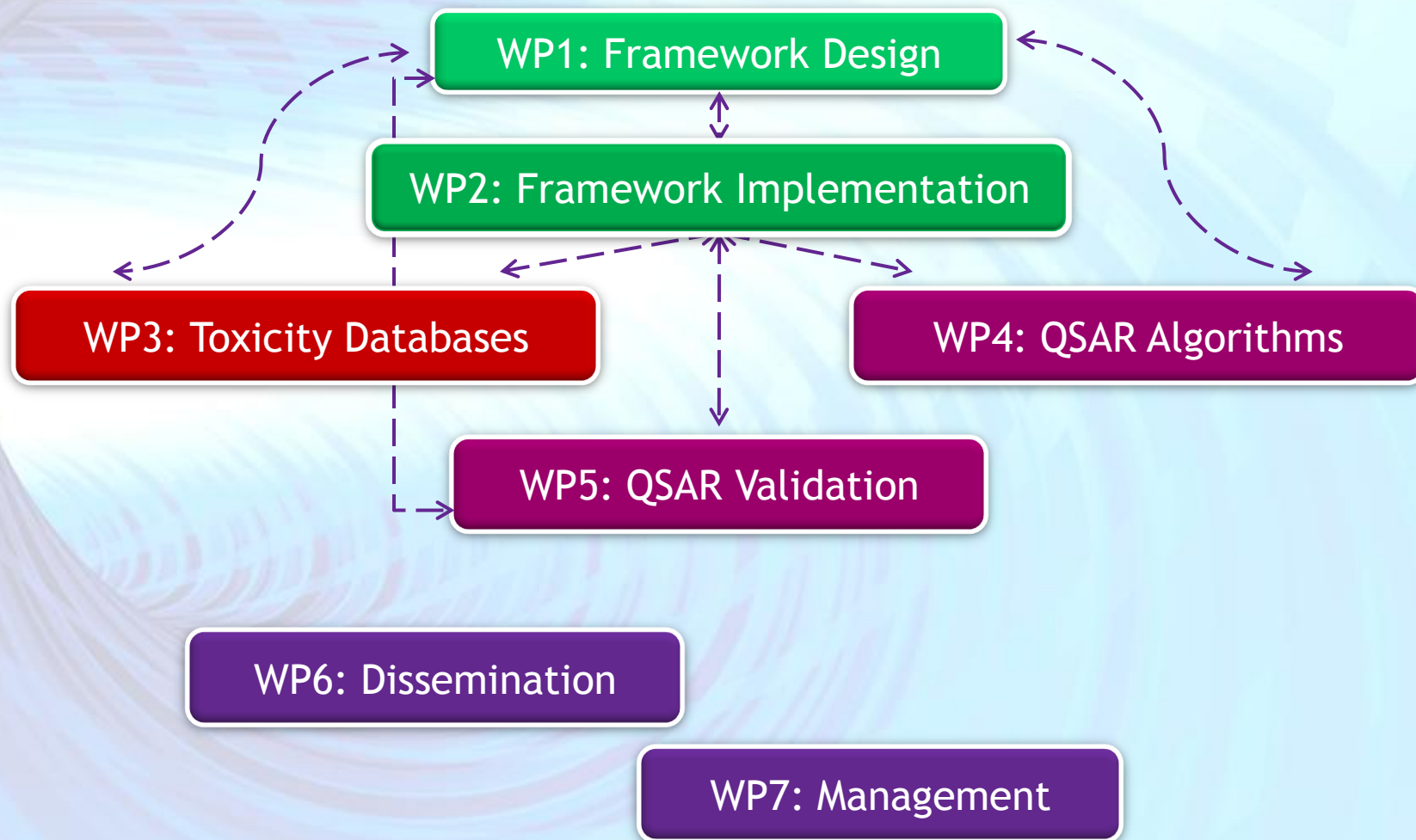
Largest number of test animals will be required for chronic and reproductive toxicity, mutagenicity, carcinogenicity endpoints because no alternative *in vitro* assays currently available

# Initiation of OpenTox

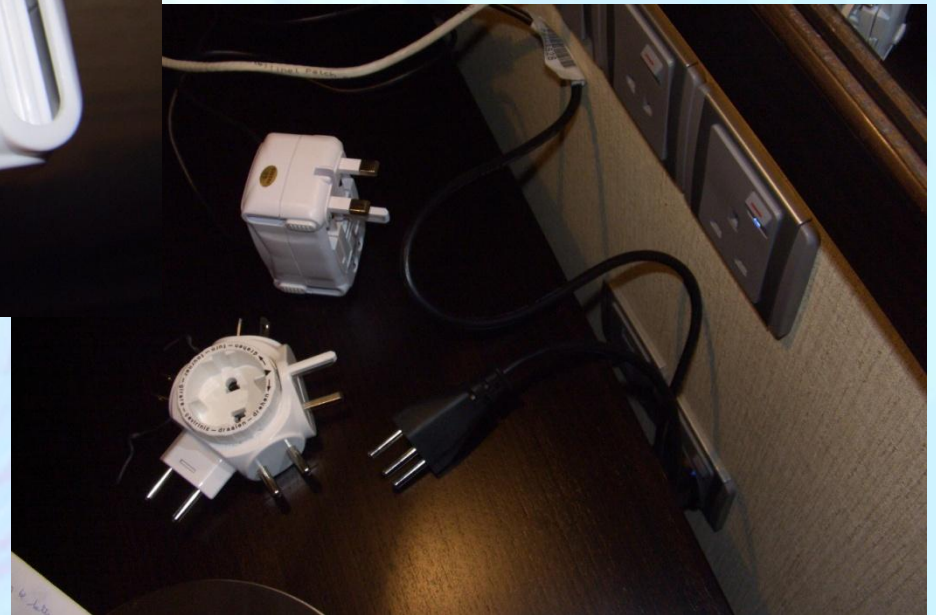
- **EC FP7 Funded - started September 2008**
- **Initial research has defined:**
  - essential components for framework architecture
  - approach to data access, schema and management
  - use of controlled vocabularies and ontologies
  - web service and communications protocols
  - selection & integration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



# Introduction - OpenTox Work Packages



# Interoperability





# Interoperability



# Interoperability





# 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

# OpenTox Framework - Standards

## Minimum Information Standards for Biological Experiments

[en.wikipedia.org/wiki/Minimum\\_Information\\_Standards](http://en.wikipedia.org/wiki/Minimum_Information_Standards))

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

## Toxicity Data

- DSSTox [www.epa.gov/ncct/dsstox/](http://www.epa.gov/ncct/dsstox/)
- ToxML [www.leadscope.com/toxml.php](http://www.leadscope.com/toxml.php)
- PubChem [pubchem.ncbi.nlm.nih.gov/](http://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](http://www.oecd.org/document/13/0,3343,en_2649_34365_36206733_1_1_1_1,00.html)
- IUCLID5 templates  
[iuclid.eu/](http://iuclid.eu/)

# 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](http://www.oecd.org/dataoecd/33/37/37849783.pdf)
- QSAR Model Reporting Format (QMRF)  
[qsar.db.jrc.it/qmrf/help.html](http://qsar.db.jrc.it/qmrf/help.html)
- QSAR Prediction Reporting Format (QPRF)  
[ecb.jrc.it/qsar/qsar-tools/qrf/QPRF\\_version\\_1.1.pdf](http://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](http://guidance.echa.europa.eu/guidance_en.htm)



# OpenTox Framework - Components

## Component Descriptions

- See [OpenTox.org](http://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

# 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

# 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



# 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 ([http://en.wikipedia.org/wiki/Representational\\_State\\_Transfer](http://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})`

# 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
```

# OpenTox Framework - API 1.1

- Initial versions of APIs (*fairly*) complete for:
  - Compound
  - Algorithm
  - Dataset
  - Model
  - Task
  - Validation
- Others on reporting, ontology, authentication are more work in progress
- First two development iterations ca. 5 months completing end of November 09. Moving to 6 weeks iterations for 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...



# 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

# 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

# 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

# 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

# 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.



# OpenToxipedia

- New OpenTox Community based Vocabulary Initiative
- Resource Location: <http://www.opentox.org/opentoxipedia>
- 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 definition edits or additional information to entries in the resource
- OpenToxipedia provides here a Vocabulary Resource of toxicology terminology
- Intend to extend to cover new emerging vocabulary for alternative *in vitro* toxicology assays
- Include vocabulary meeting regulatory reporting requirements in alternative testing

# 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.

	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

# 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](http://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



# 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

# 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

# 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

# OpenTox Use Cases - Class 3 level (b)

## Category C Validation

- 3.C.1 Validate an SVM 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

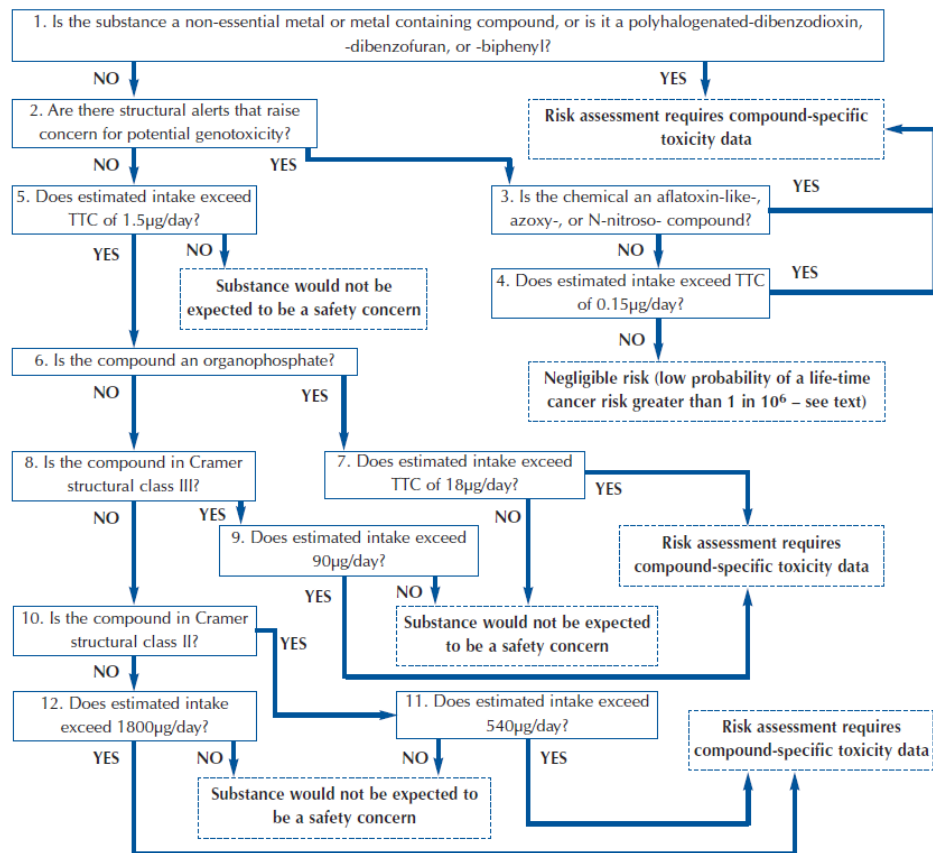
## Category D Reporting

- 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

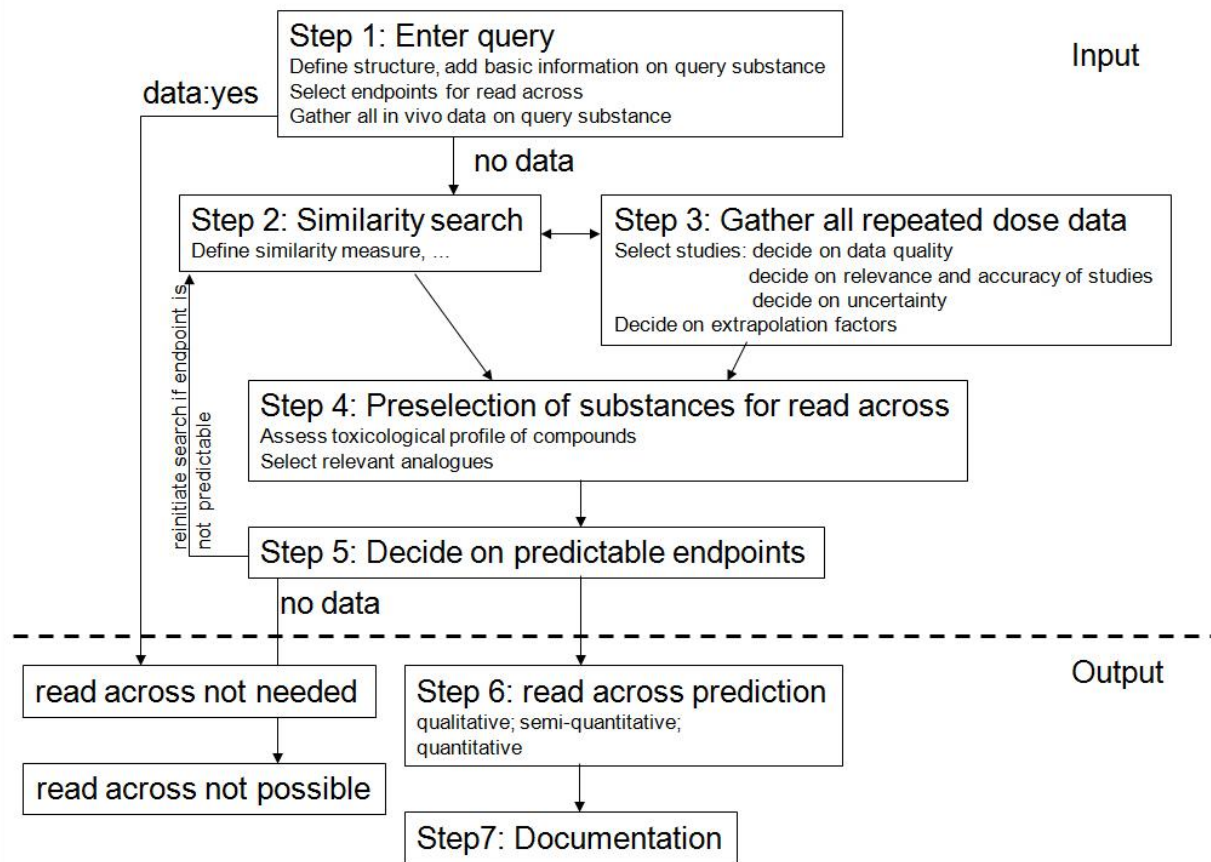


# OpenTox Use Case - implement Threshold of Toxicological Concern (TTC) using ILSI decision tree guidelines

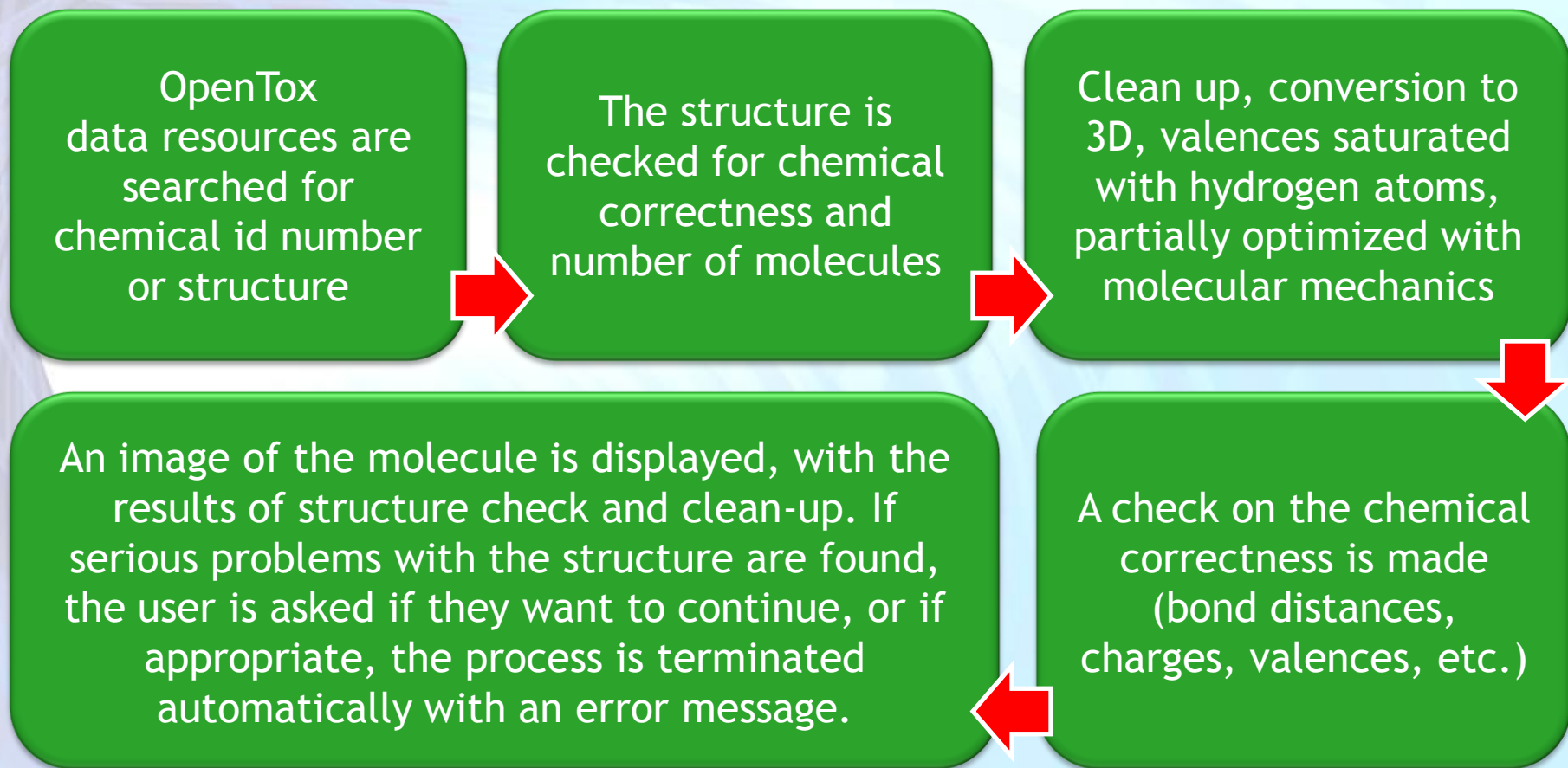
Decision tree proposed by ILSI Europe to decide whether substances can be assessed by the TTC approach  
(From Kroes *et al.*, *Food and Chemical Toxicology* 42, p76, 2004)



# OpenTox Use Case - Read Across for Repeated Dose Toxicity



# OpenTox Use Case - given a structure, predict endpoints



# OpenTox Use Case - given a structure, predict endpoints

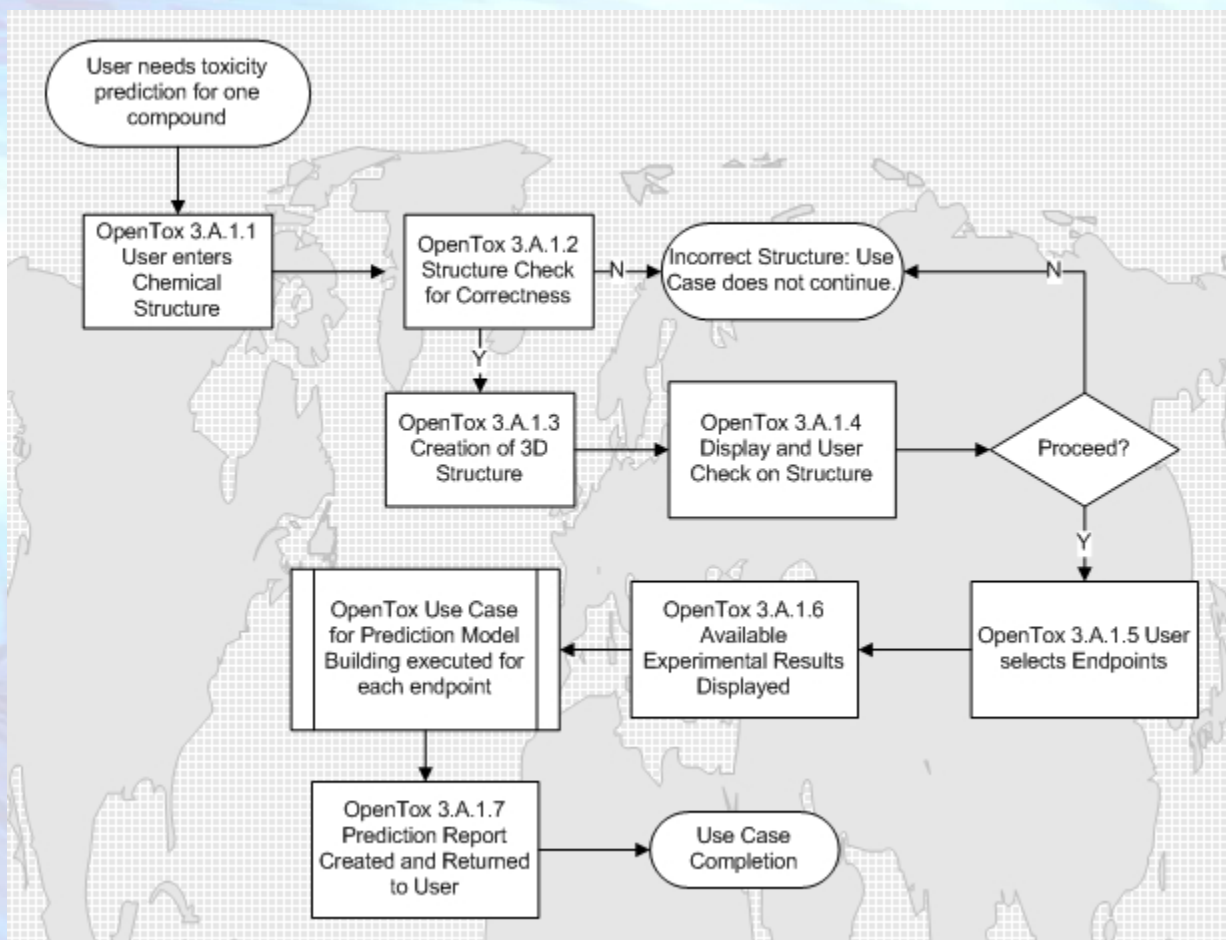
If experimental results for the molecule are found in the database, then the following is printed "Experimental data for this structure is available in the OpenTox database and is summarized here:"

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

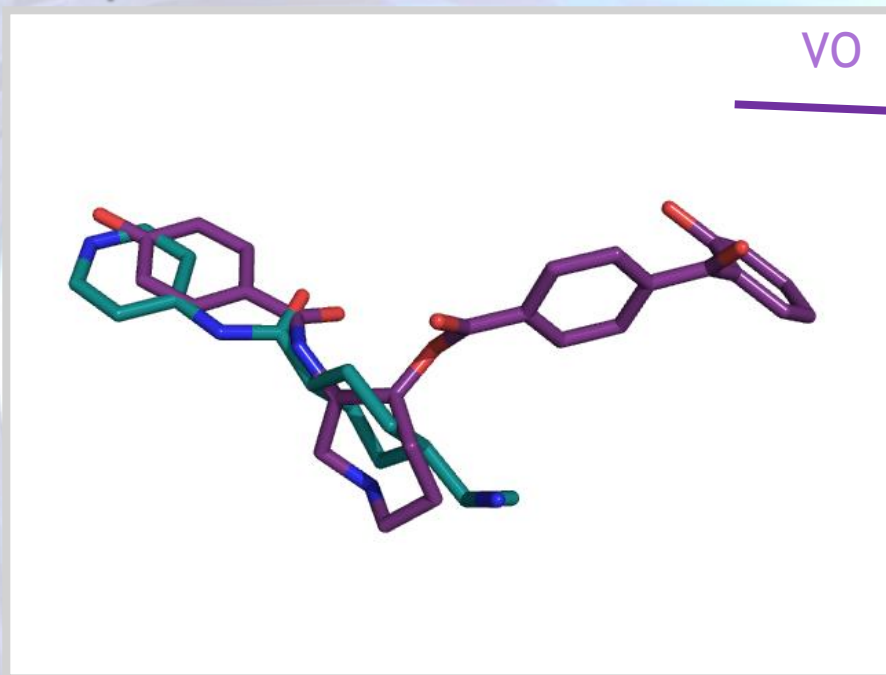
The prediction report is provided including the details of the basis for model prediction and including statistical reporting on the reliability of the prediction



# 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
- ☐ Reproductive Toxicology
- ☐ Skin Irritation
- ☐ Aqua Toxicity
- ☐ Combined predictions for arrays of multiple end points



Business Driver

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

Our situation  
today. When we  
ask..

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







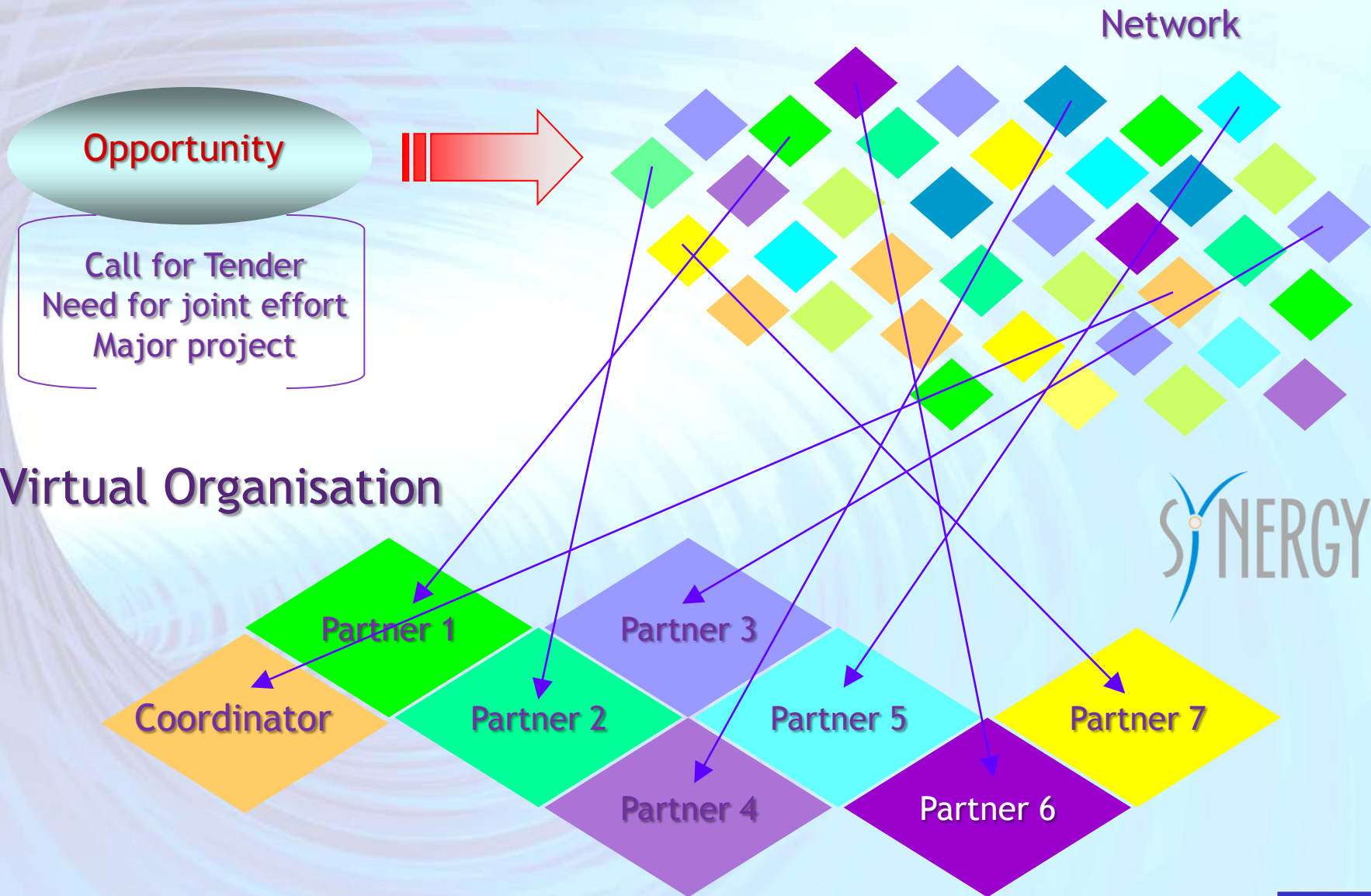
**And is it not clear what we need and should do, but...?**



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



# Creating Collaborations



S NERGY

# Creating and Operating Collaborations

## Opportunity

Call for Tender  
Need for joint effort  
Major project

## Virtual Organisation



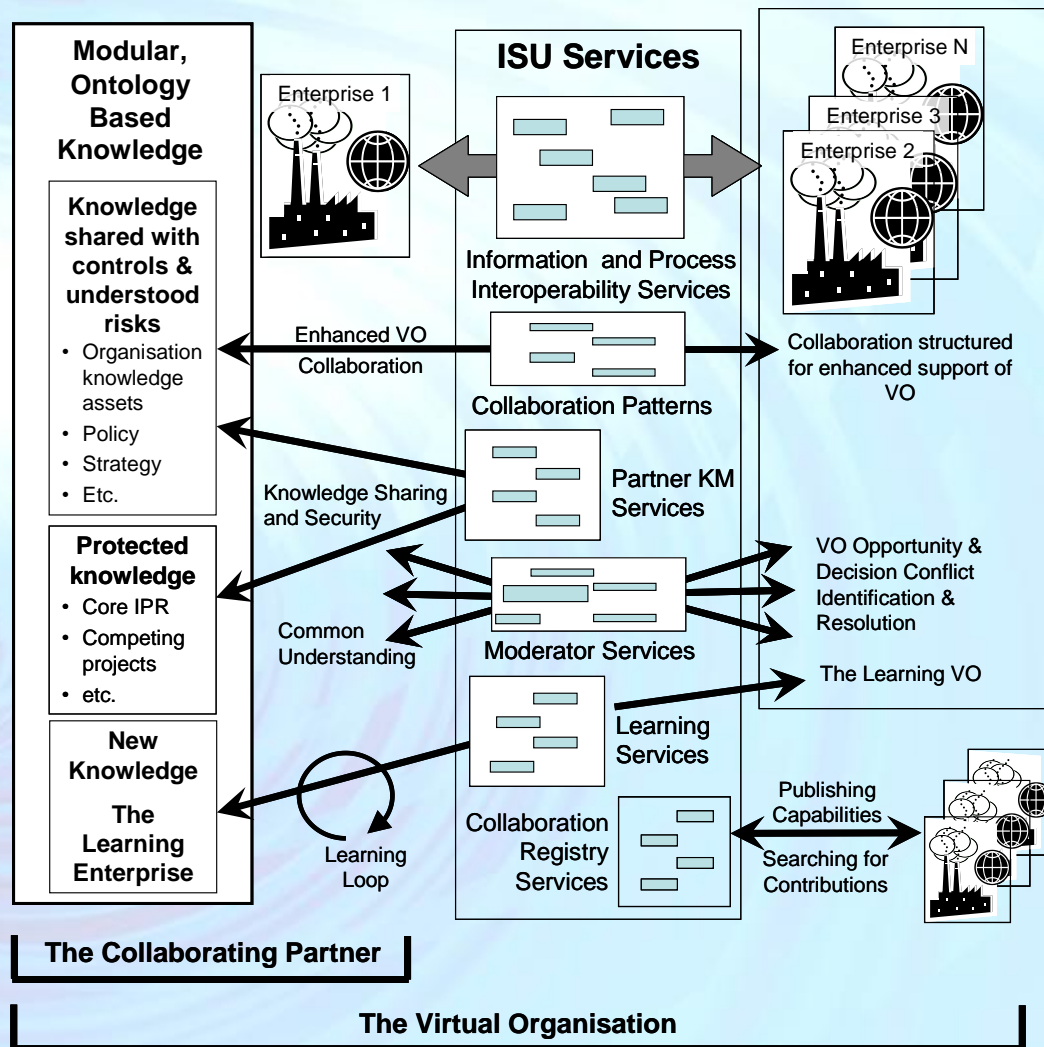
SYNERGY



# Building Collaborations - SYNERGY

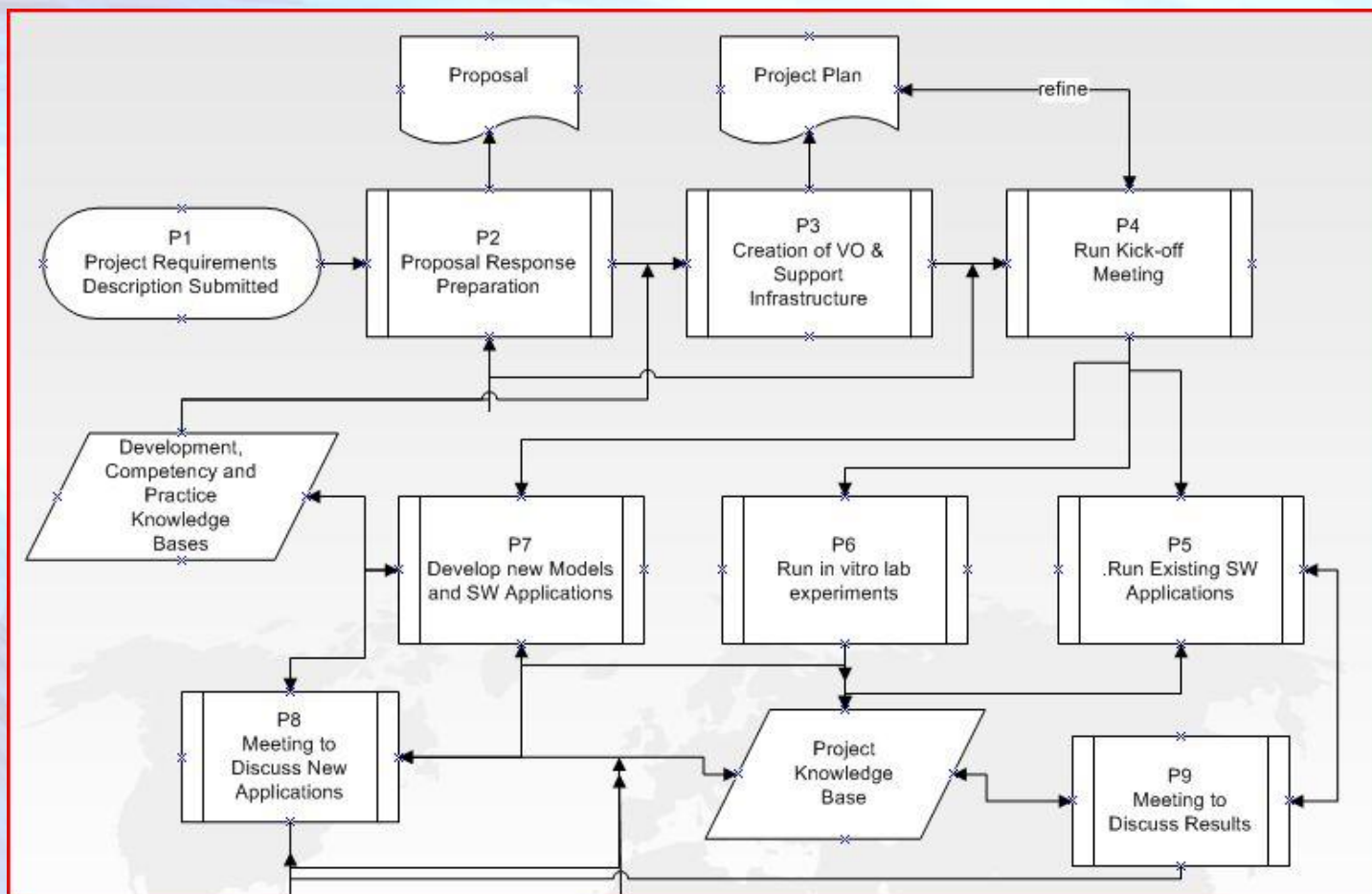


SYNERGY website:  
<http://www.synergy-ist.eu/>

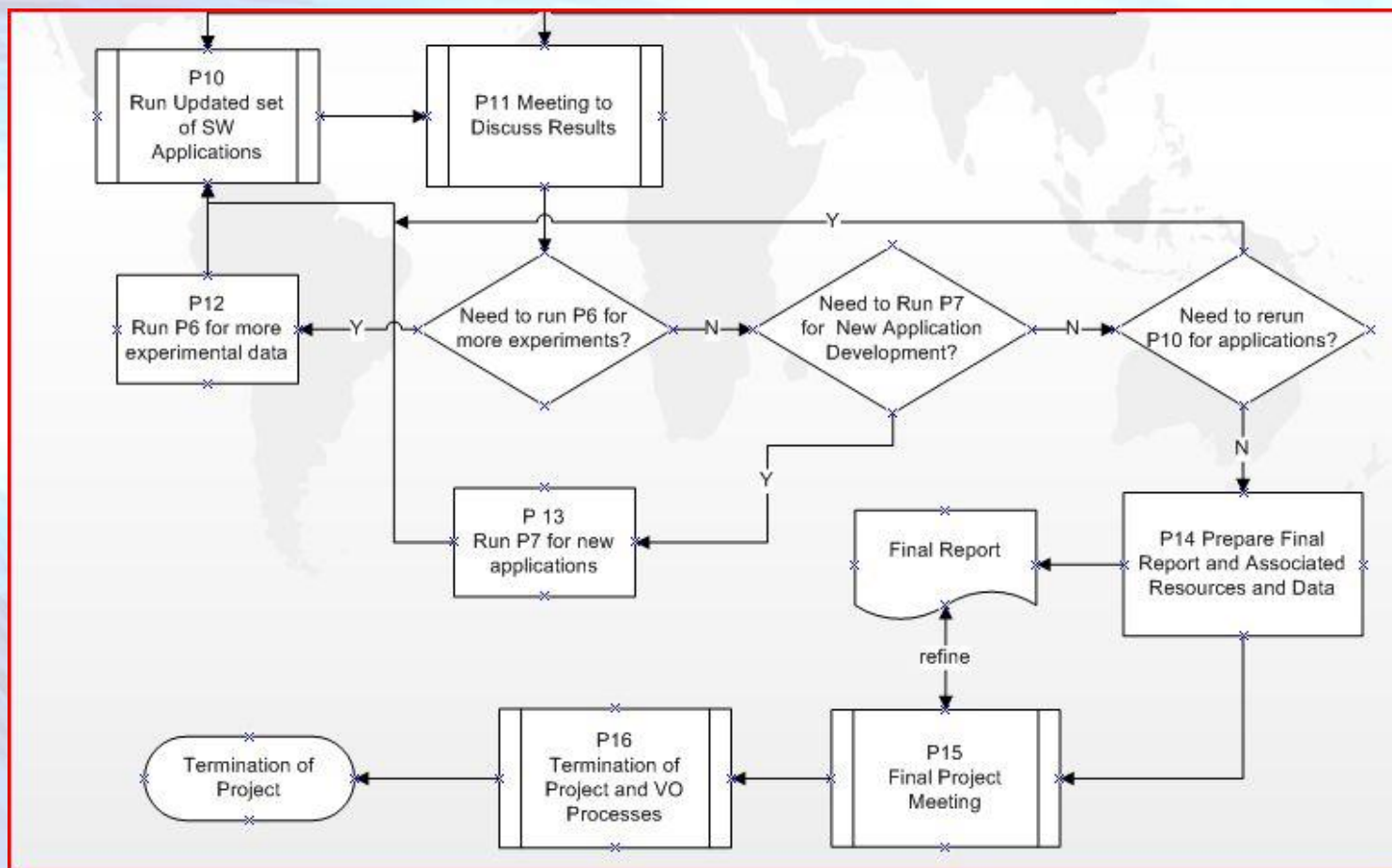




# Collaborative Predictive Toxicology VO Workflow



# Collaborative Predictive Toxicology VO Workflow



# 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 Spring 2010

# 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



# 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](#)

# Prediction of ToxRefDb *in vivo* data with existing models (including lazarus 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. Jeliaskova, 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

# Prediction of ToxRefDb *in vivo* data with existing models (including lazarus 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. Jeliaskova, 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

# Prediction of ToxRefDb *in vivo* data with existing models (including lazarus 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. Jeliaskova, 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



# Prediction of ToxRefDb *in vivo* data with existing models (including lazarus 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

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

- Toxtree::Verhaar scheme (toxicity mode of action)

- Verhaar H.J.M., Van Leeuwen 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

# 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 and combine with other modelling approaches, methods, practices to handle such datasets
- We need to be able to handle complex and flexible collaborative workflows on co-working on such problems (has become an OpenTox Use Case)

# 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*



# 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
- 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 at [www.opentox.org](http://www.opentox.org))

# Acknowledgements - OpenTox Partners

In Silico Toxicology,  
Switzerland

Ideaconsult,  
Bulgaria

Istituto Superiore  
di Sanità, Italy

Technical University  
of Munich, Germany

David Gallagher, UK

Douglas Connect,  
Switzerland

Albert Ludwigs University  
Freiburg, Germany

National Technical  
University of Athens,  
Greece

Fraunhofer Institute  
for Toxicology &  
Experimental Medicine,  
Germany

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

Seascope Learning,  
India



# Acknowledgements - Co-workers

Barry Hardy  
Nicki Douglas  
Christoph Helma  
Michael Rautenberg  
Nina Jeliaskova  
Vedrin Jeliaskov  
Luben Boyanov  
Chelsea Jiang  
Martin Martinov  
Romualdo Benigni  
Olga Tcheremenskaia  
Stefan Kramer  
Tobias Girschick

Fabian Buchwald  
Jörg Wicker  
Andreas Karwath  
Martin Gütlein  
Andreas Maunz  
Haralambos Sarimveis  
Georgia Melagraki  
Antreas Afantitis  
Pantelis Sopasakis  
David Gallagher  
Vladimir Poroikov  
Dmitry Filimonov  
Alexey Zakharov  
Alexey Lagunin

Tatyana Gloriovova  
Sergey Novikov  
Natalia Skvortsova  
Sunil Chawla  
Steve Bowlus  
Indira Ghosh  
Surajit Ray  
Gaurav Singhai  
Om Prakash  
Sylvia Escher  
Sara Weiss

# 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



# Final words...

Visit the OpenTox website for  
more information at

[OpenTox.org](http://OpenTox.org)

Contact me:

barry.hardy -(at)- douglasconnect.com

Many thanks for your  
attention!



OpenTox - An Open Source Predictive Toxicology Framework, [www.opentox.org](http://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).