OpenTox Overview

CADASTER virtual meeting

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OpenTox

SEVENTH FRAMEWORK PROGRAMME

Motivation

- Predictive Toxicology applications need **common components**:
  - Access to datasets
  - Algorithms for descriptor calculation and model building
  - Validation routines
- These components have to be re-implemented for every new application
- If we had these components readily available we could
  - Quickly build new applications for specific purposes
  - Experiment with new combinations of algorithms
  - Speed up method development and testing
  - …

OpenTox Components

- **Compounds**: Structures, names, …
- **Features:** Chemical and biological (toxicological) properties, substructures, …
- **Datasets:** Relationships between compounds and features
- **Algorithms**: Instructions for solving problems
- **Models:** Algorithms applied to data yield models, which can be used for predictions
- **Validation**: Methods for estimating the accuracy of model predictions
- **Reports:** Report predictions and models, e.g. to regulatory authorities
- **Tasks:** Handle long running calculations
- **Authentication and Authorization**: Protect confidential data
- **Service registration** and querying : Finding services of specific type

Requirements

- Platform independency
- Interoperability for communication with external programs and data sources
- Transparency for scientific and regulatory credibility
- Open for future extensions

Technological choices

- Web services
- Communication through well defined interfaces
- Ontologies for the exchange of knowledge and data
- Use and promote open standards
- Open source components

REpresentational State Transfer (REST)

- What?
  - Architectural style for distributed information systems on the Web
  - Simple interfaces, data transfer via **hypertext transfer protocol (HTTP)**, stateless client/server protocol
    - GET, POST, PUT, DELETE
  - Each **resource** is **addressed** by its own **web address**
- Why?
  - **Lightweight** approach to **web services**
  - **Simplifies/enables** development of **distributed and local** systems
  - Language independent

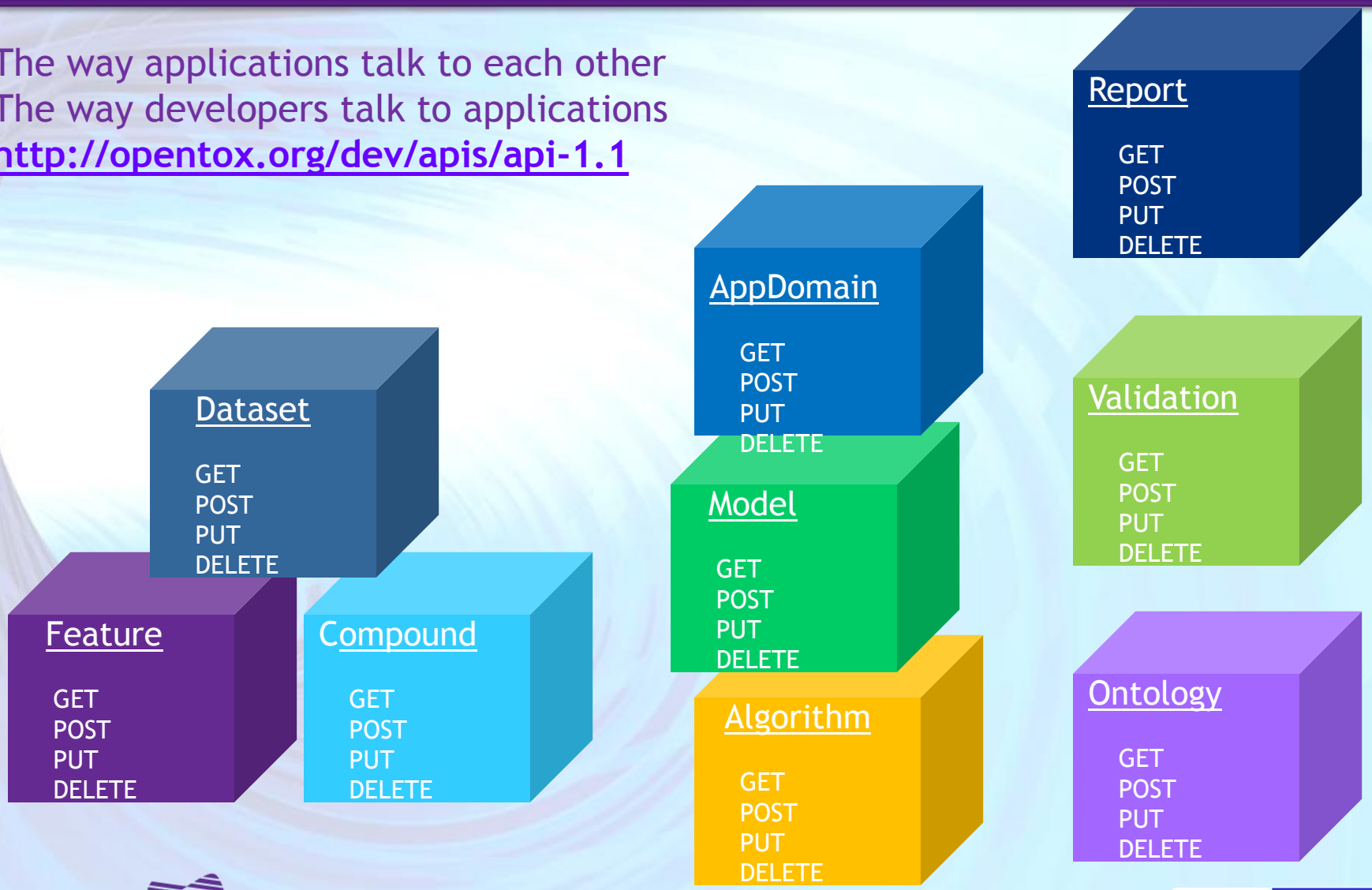
Resources identification

All resources are identified via unique web address, assigned according to the URL templates

Component	Description	URL Template (example)
Compound	Representations of chemical compounds	http://host:port/compound/{compoundid}
Feature	Properties and identifiers	http://host:port/feature/{featureid}
Dataset	Encapsulates set of chemical compounds and their property values	http://host:port/dataset/{datasetid}
Model	OpenTox model services	http://host:port/model/{modelId}
Algorithm	OpenTox algorithm services	http://host:port/algorithm/{algorithmid}
Validation, Report	A validation corresponds to the validation of a model on a test dataset.	http://host:port/validation/{validationid} http://host:port/report/{reportid}
Task	Asynchronous jobs are handled via an intermediate Task resource. A resource, submitting an asynchronous job should return the URI of the task.	http://host:port/task/{taskid}
Ontology service	Provides storage and SPARQL search functionality for objects, defined in OpenTox services and relevant ontologies	http://host:port/ontology
Authentication and authorisation	Granting access to protected resources for authorised users	http://host:port/opensso http://host:port/opensso-pol

OpenTox API (Application Programming Interface)

- The way applications talk to each other
- The way developers talk to applications
- http://opentox.org/dev/apis/api-1.1



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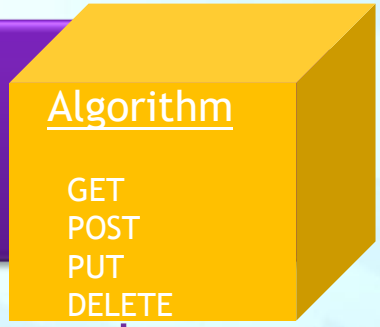
SEVENTH FRAMEWORK PROGRAMME

Services implementation by partner and service type

All components are implemented as REST web services.
There could be multiple implementations of same type of components.
(Subset of) services could be hosted by the same provider, or by multiple providers on separate locations.

Partner No. /Service type	Compound	Dataset	Feature	Algorithm (processing)	Algorithm (model)	Model	Validation	Report	Task	Autherntication and Authorisation service	Ontology service
2	Y	Y		Y	Y	Y			Y		
3	Y	Y	Y	Y	Y	Y			Y		Y
5				Y	Y	Y					
6							Y	Y	Y	Y	
7					Y	Y			Y		
10						Y					

Algorithms



- Algorithms for **descriptor calculation**: **generation** and **selection** of **features** for the representation of chemicals (structrue based features, chemical and biological properties);
- **Classification** and **regression** algorithms for creation of (Q)SAR models;
- **Rule based** algorithms;
- Algorithms for the **aggregation** of predictions from multiple (Q)SAR models and endpoints, and aggregation of predictions;
- **General purpose algorithms** (e.g. for visualization, similarity and substructure queries, applicability domain, read across, …)

Algorithms : Descriptors and feature selection

- **Descriptor calculation**: services based on
  - OpenBabel
  - Joelib2
  - CDK
  - Multi-level neighborhood of atoms (MNA)
  - Substructure/fragment generation
  - MOPAC
- **Feature selection**
  - Services for feature selection based on **information gain**
  - Service for feature selection based on **Chi^2** statistics
  - **PCA**
  - **Filter** pipeline for **preprocessing**: combining approaches for handling missing values, feature seleciton, …

Algorithms

Classification/SAR

- Simple baseline: k-Nearest neighbor
- Machine learning algorithms
  - Decision trees (J48)
  - Support Vector machines (SVM)
- Probabilstic / graphical models
  - Bayesian network
  - Gaussian process regression

Regression /QSAR

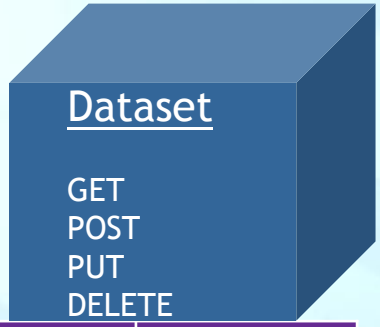
- Simple baseline: k-Nearest neighbor
- Classical statisticsl algorithms
  - Multiple linear regression (MLR)
  - Partial Least squares (PLS)
- Machine Learning algorithms
  - Model trees (M5)
  - Support vector regression
- Probabilistic/graphical models:

Rule based

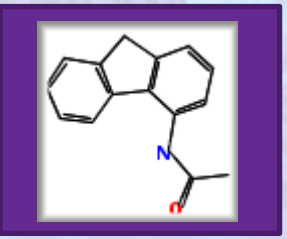
- Toxtree

Datasets
upload, read, modify, delete, search

Uniform access to data: described by W3C RDF (Resource Description framework)



Compound/ Data	http://myhost.com/feature/21580	http://myhost.com/feature/21589	http://myhost.com/feature/21573	http://myhost.com/feature/21576	http://myhost.com/feature/21588	http://myhost.com/feature/21858	http://myhost.com/feature/22114
http://myhost.com/compound/413	N,N-dimethyl-4-aminoazobenzene	CN(C1=CC=C(C=C1)N=N/C2=CC=CC=C2)C	3	3.31	225.3	YES	3.123
http://myhost.com/compound/44497	4-acetamidofluorene	O=C(Nc3					
...	...						



http://myhost.com/feature/21573

http://myhost.com/feature/21858

http://myhost.com/feature/22114
a ot:Feature , ot:NumericFeature ;
dc:creator
"http://www.blueobelisk.org/ontologies/chemoinformatics-algorithms/#xlogP" ;
dc:title "XLogP" ;
ot:hasSource
<http://myhost.com/algorithm/org.openscience.cdk.qsar.descriptors.molecular.XLogPDescriptor> ;
= otee:Octanol-water_partition_coefficient_Kow .

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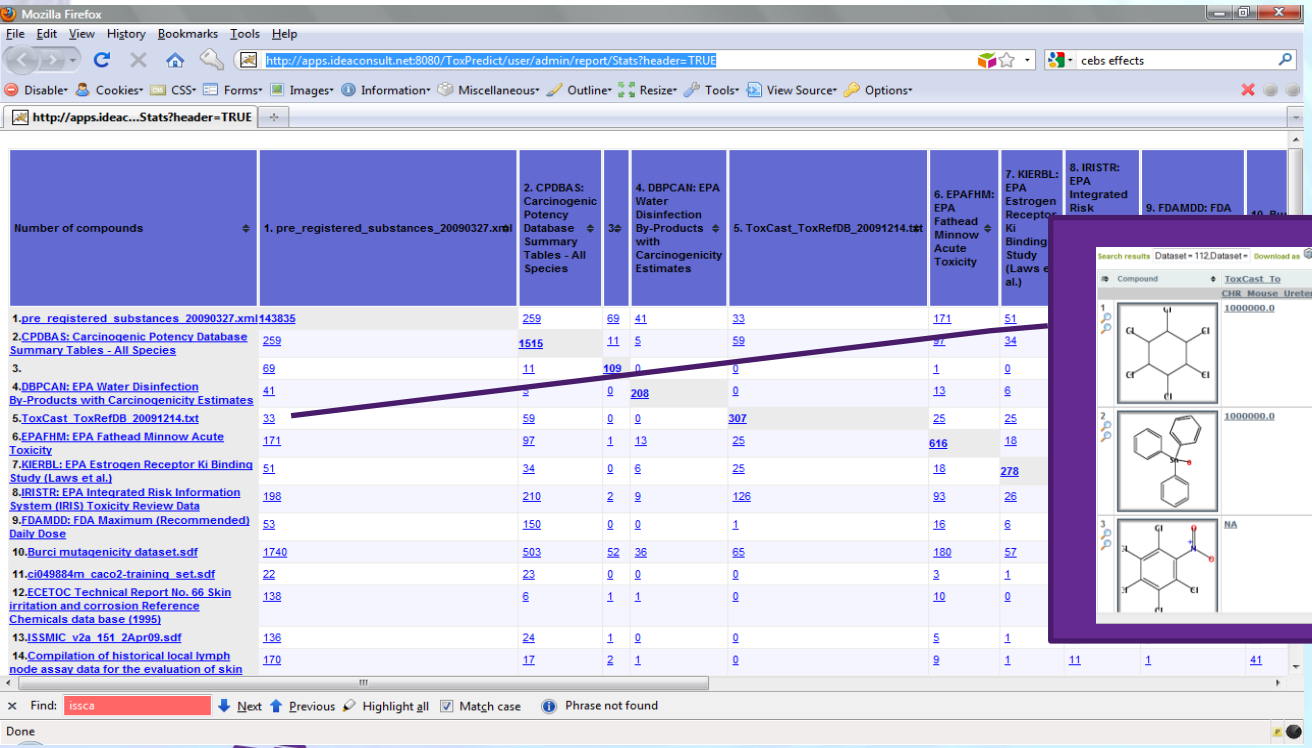
Uniform access to the data

- Datasets can be easily merged, compared , and calculations reproduced, regardless of their physical place.
- The dataset service offers property, compound, substructure and similarity searches via uniform OpenTox Application Programming



Ontologies

- What?
  - **Formal, shared conceptualization** of a **domain**
- Why?
  - Distributed services **need** to be able to "talk to each other", e.g. have a **common understanding** of endpoints, properties, methods, etc.
  - Allows us to integrate existing knowledge from many related domains

Ontologies

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

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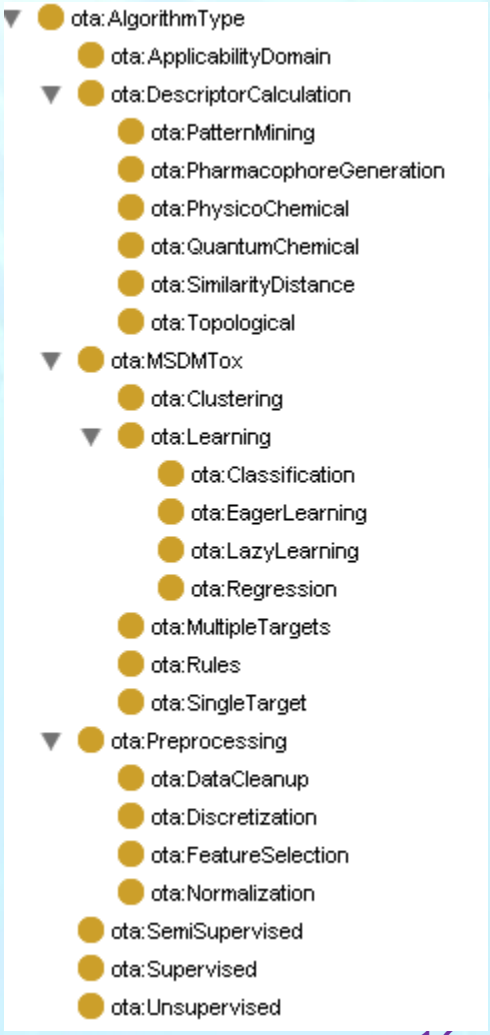
Ontology Working Group



Toxicological data: needs for standards

- Needs for data standards for automatic data integration
  - Example: **Carcinogenic Activity**

CPDBAS: Carcinogenic Potency Database
http://www.epa.gov/ncct/dsstox/sdf_cpdbas.html#SDFFields

ISSCAN: Chemical Carcinogens Database
http://www.iss.it/ampp/dati/cont.php?id=233&lang=1&tipo=7

ActivityOutcome
active
unspecified/blank
inactive

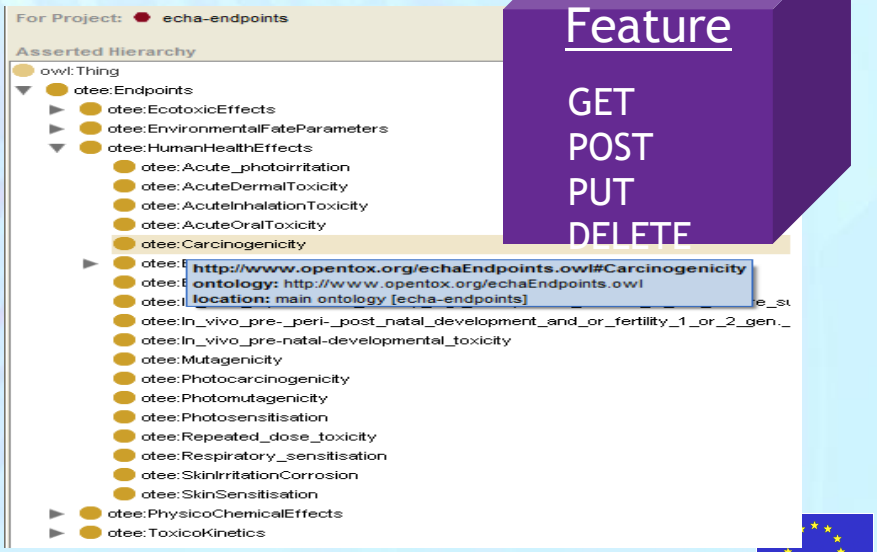
Integration

Canc
3 = carcinogen;
2 = equivocal;
1 = noncarcinogen

OpenTox datasets represent endpoint data as features. Features can have arbitrary names (e.g. “Canc”), but are also associated with entries from relevant ontologies.

e.g. (simplified example)

http://opentox.org/echaEndpoints.owl#Carcinogenicity



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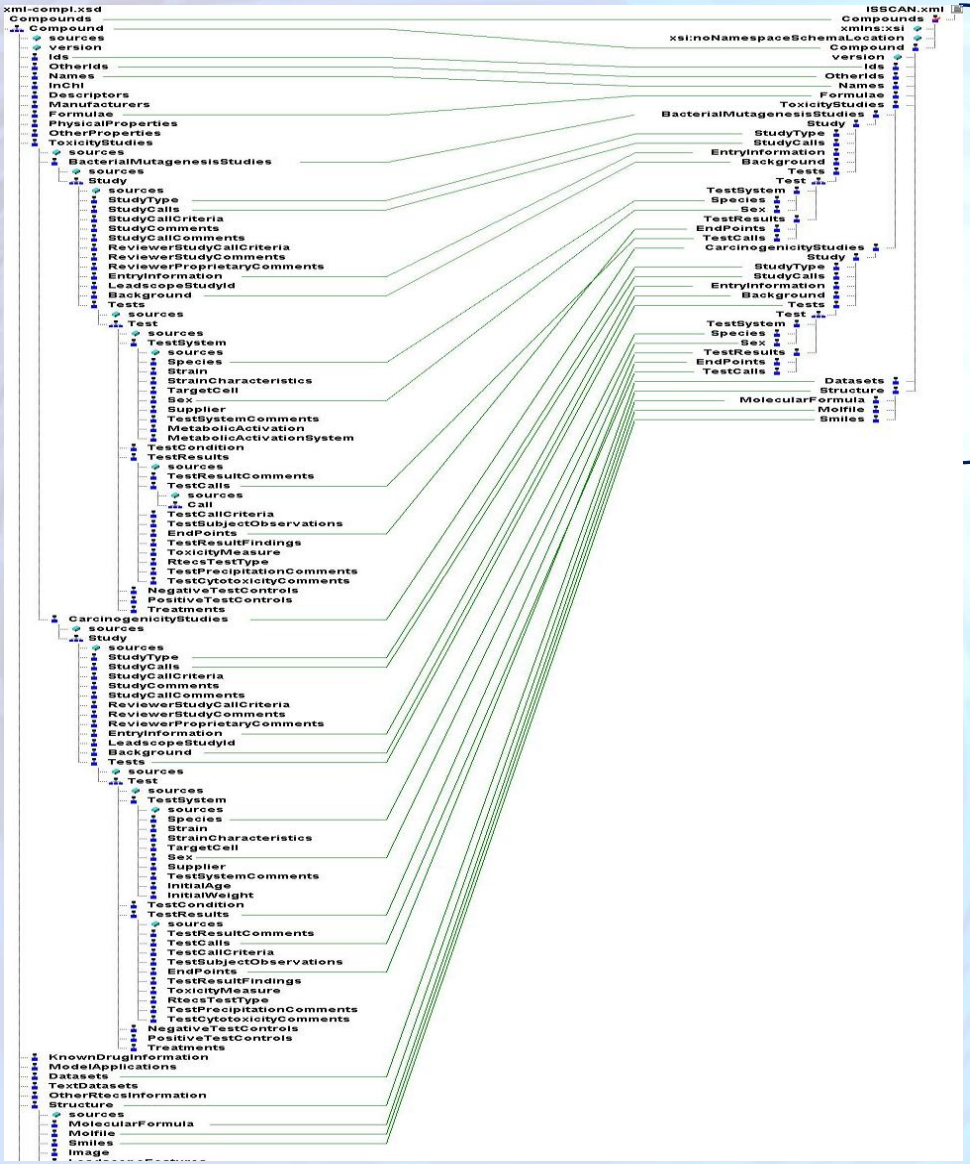
Mapping of the ISSCAN entry - ToxML xsd scheme



CAS	67-66-3
Substance ID	4
ChemName	Chloroform
Synonyms	Formyl trichloride; methane trichloride; methenyl trichloride; Methyl trichloride; R 20; r 20 (refrigerant); Refrigerant R20; trichloroform; Trichloromethane
SAL	negative
Canc	positive
Reference	CPDB
TD50_Rat	262
TD50_Mouse	90.3
Rat_Male_Canc	positive
Rat_Male_NTP	ND
Rat_Female_Canc	positive
Rat_Female_NTP	ND
Mouse_Male_Canc	positive
Mouse_Male_NTP	ND
Mouse_Female_Canc	positive
Mouse_Female_NTP	ND
MolWeight	119.38
Formula	CHCl3
SDF file	Connection table
SMILES	ClC(Cl)Cl

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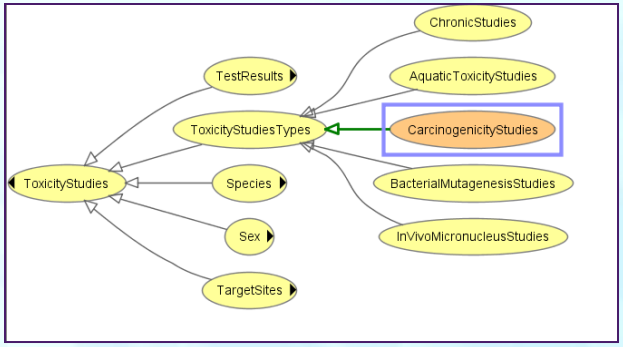
OpenTox Toxicological Endpoint Ontology

- **Why we need an ontology?**
  - Distributed services need to be able to "talk to each other", i.e. have a common understanding of endpoints, any type of property, methods, etc
- **Methodology**
  - Starting from 5 toxicological endpoints
  - following OBO Foundry principles



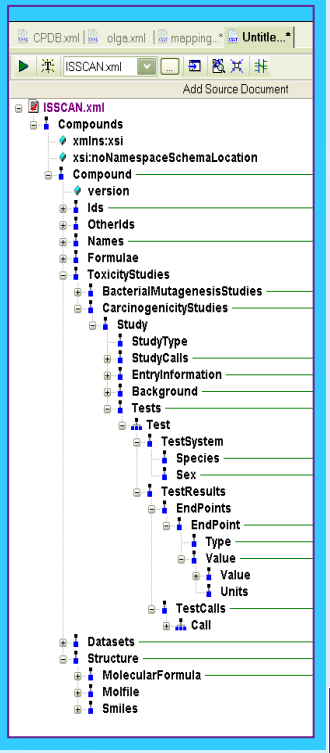
Other freely available resources: DSSTOX, GoReni (ITEM), etc

Protégé, free open source OWL (Web Ontology Language) editor

OpenTox Toxicological Data Ontology

Re-use of pieces or terms defined in neighboring ontologies (OWL and OBO)

ToxML scheme



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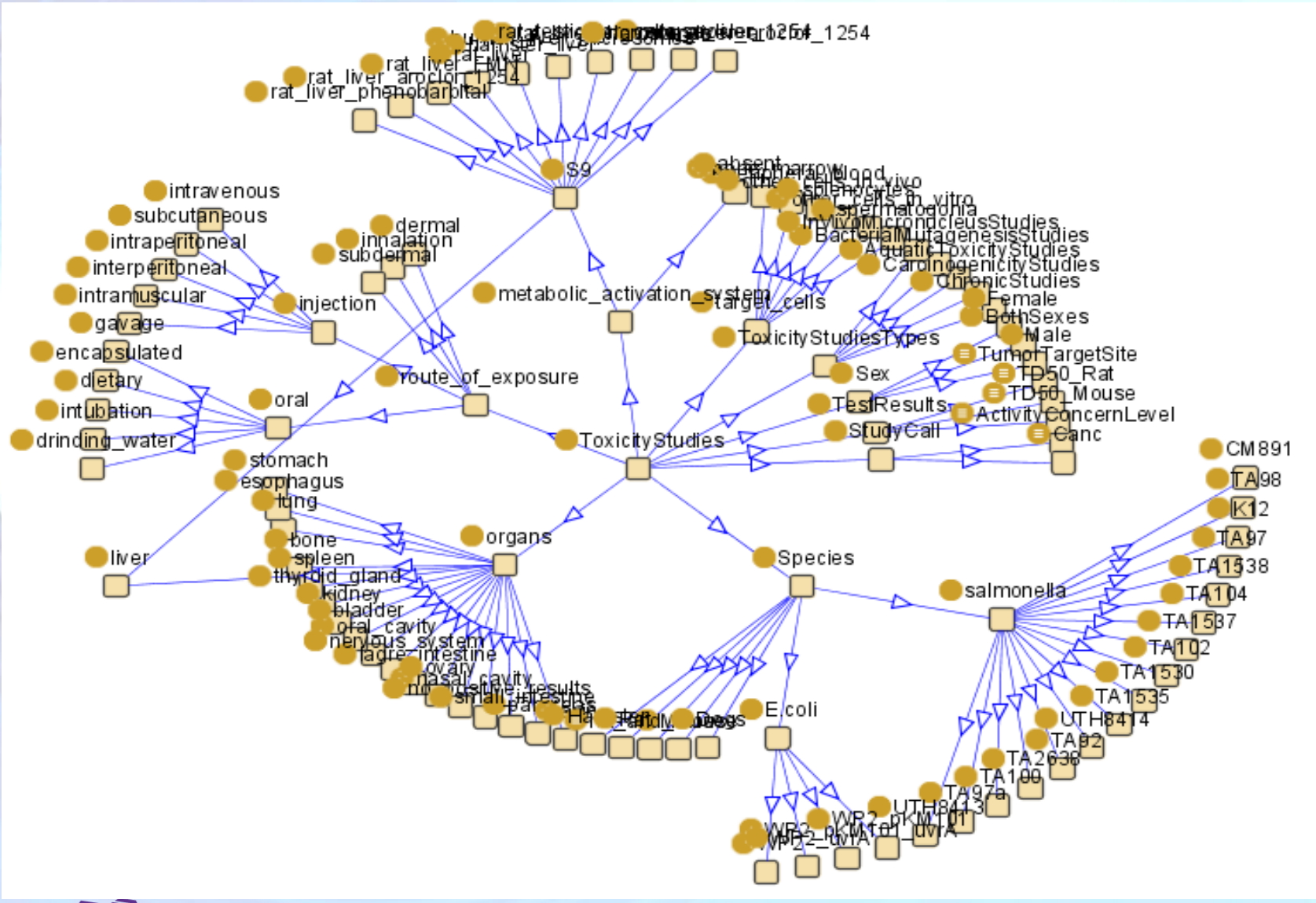
Toxicological Ontology: graphical representation



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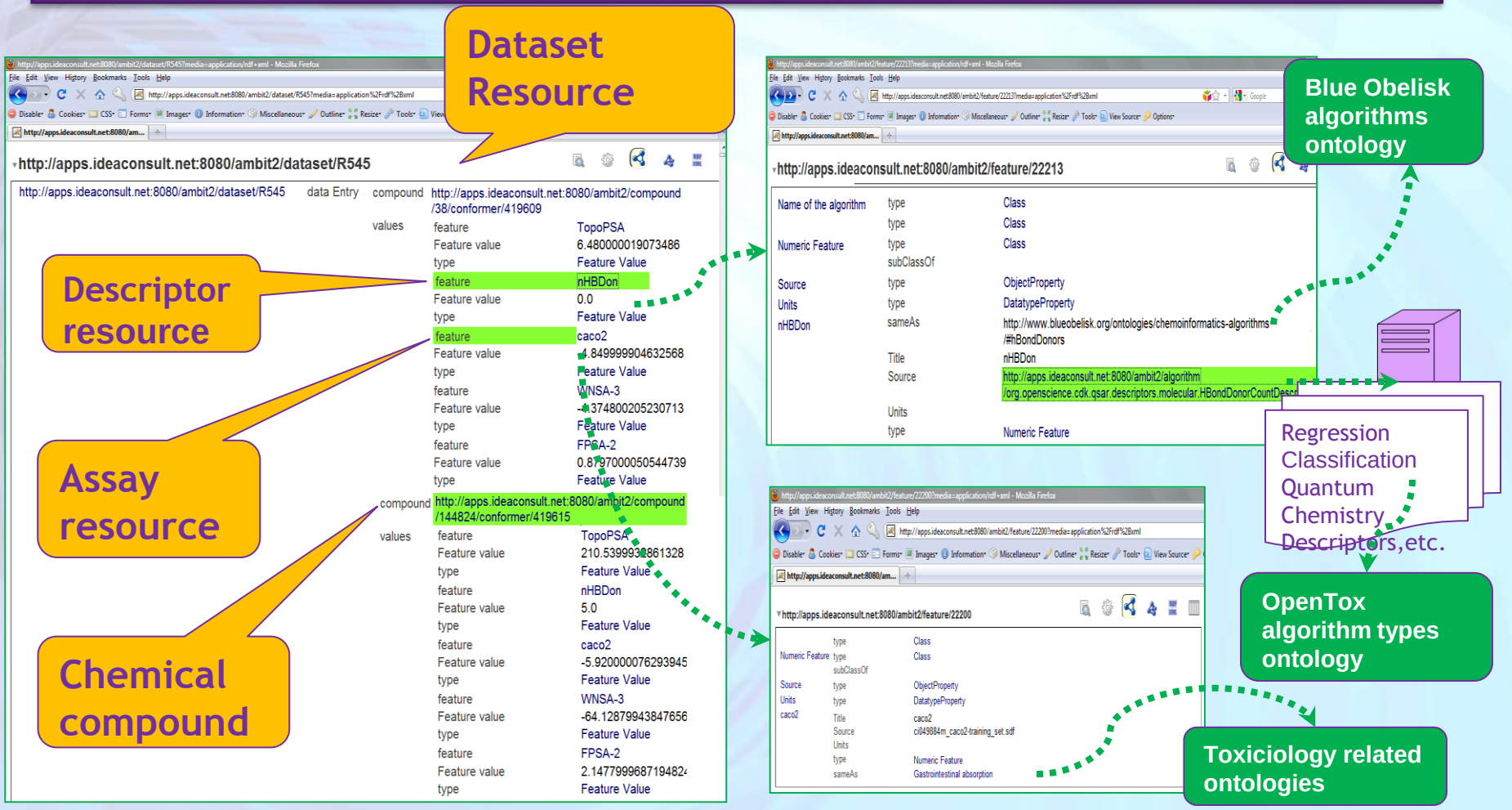
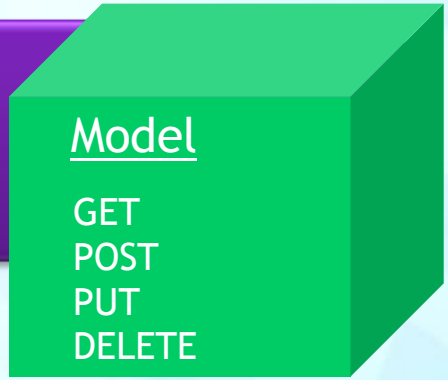
Linked resources:
Compound, Algorithm, Model, Dataset, Features



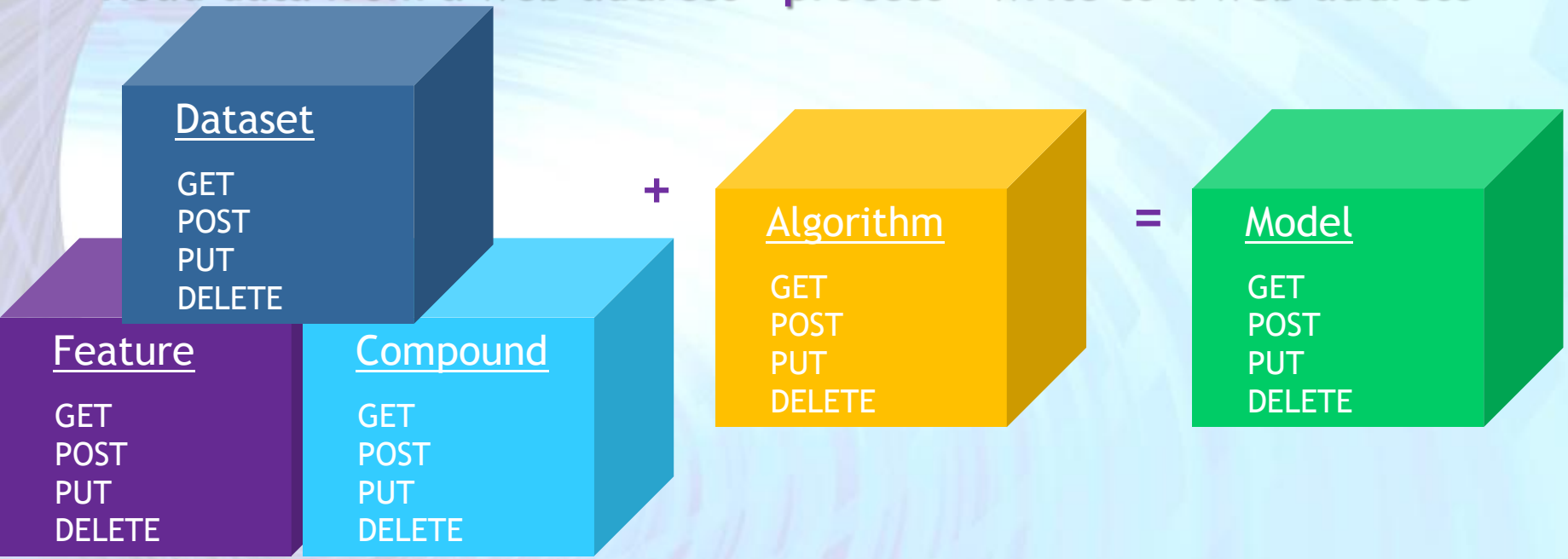
Models



- **Models:** Models are generated by respective algorithms, given specific parameters and data
  - Statistical models are generated by applying statistical/machine learning algorithms to specific dataset and parameters
  - Models can be other than statistical, e.g.
    - expert defined rules,
    - quantum mechanical calculations,
    - metabolite generation, etc.
- The intention of the framework is to be generic enough to accommodate varieties of predictive models.
- Models services provide facilities to inspect, store and delete models. Every model is identified by unique web address.

Uniform approach to models creation

Read data from a web address - process - write to a web address



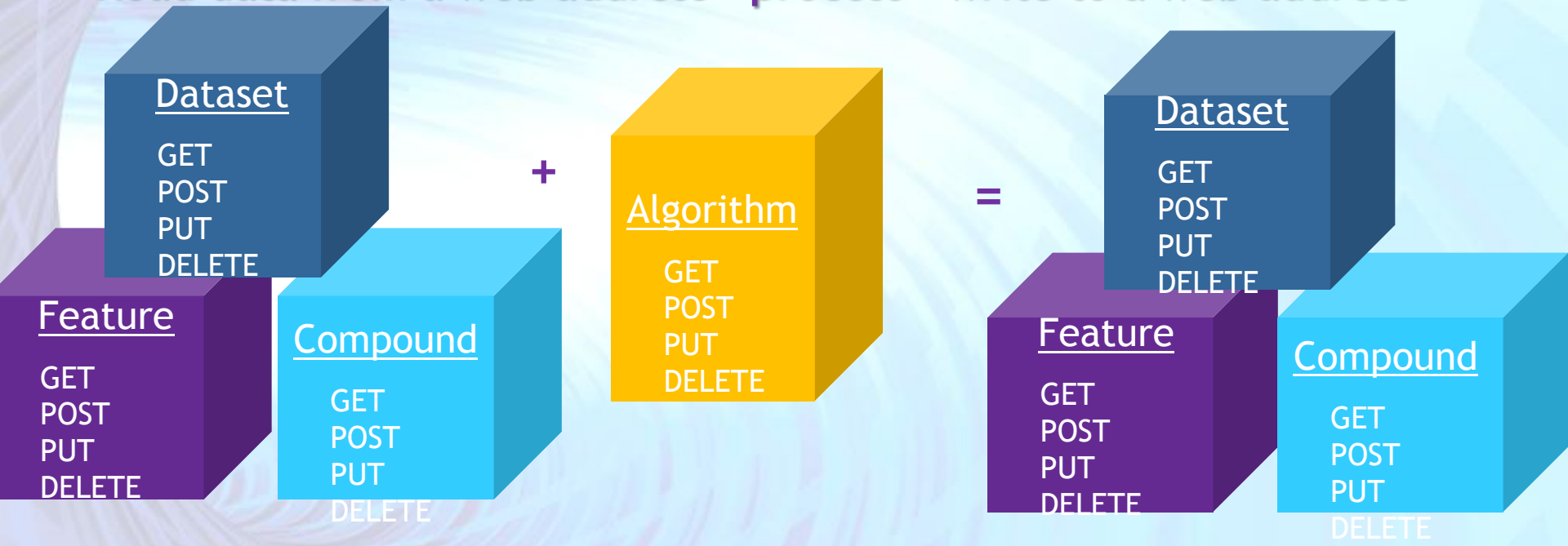
http://myhost.com/algorithm/neuralnetwork

http://myhost.com/dataset/trainingset1

http://myhost.com/model/predictivemodel1

Uniform approach to data processing (e.g. Descriptors calculation)

Read data from a web address - process - write to a web address

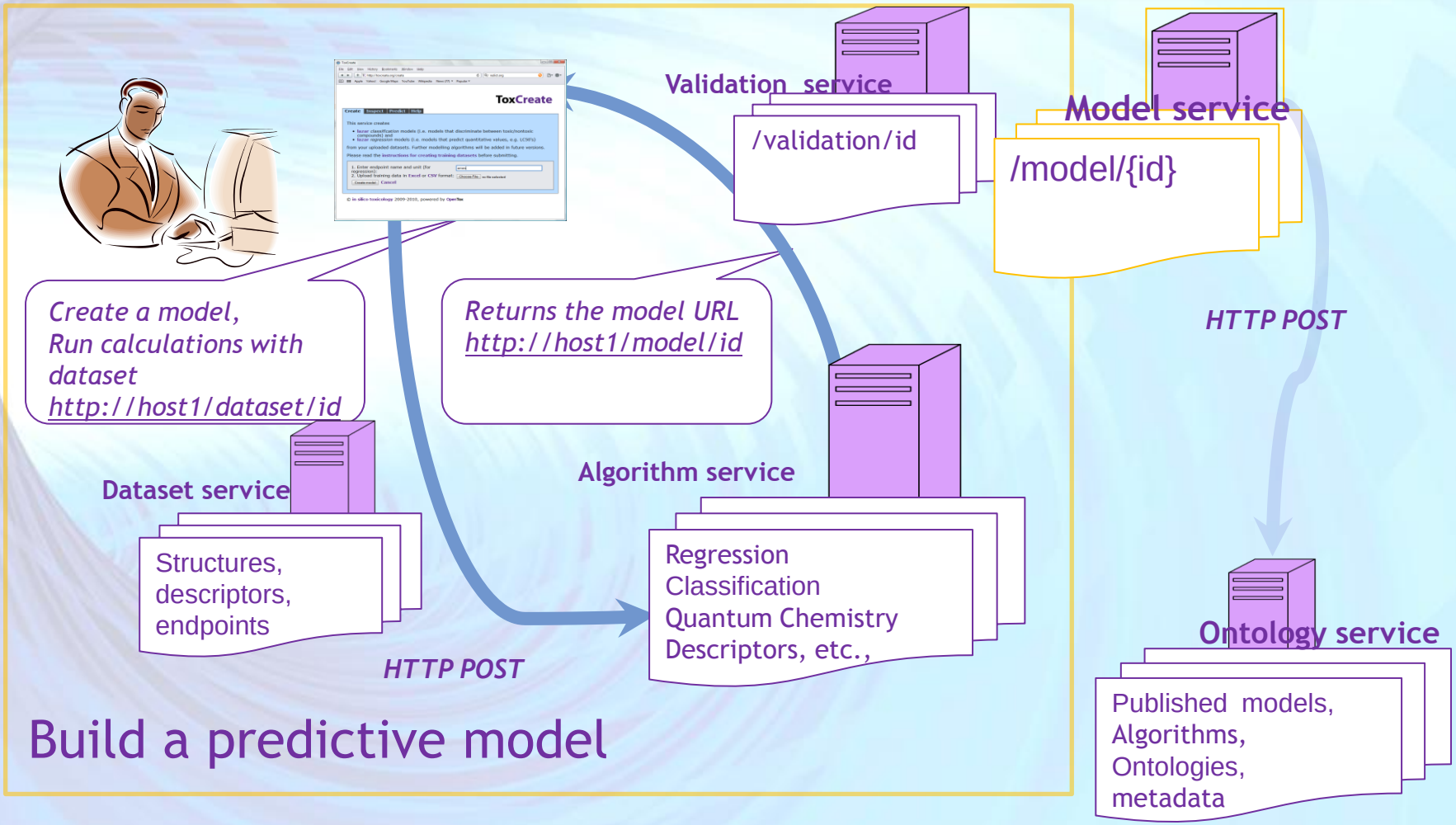


http://myhost.com/algorithm/{descriptorX}

http://myhost.com/dataset/trainingset1

http://myhost.com/dataset/results

Build a predictive model



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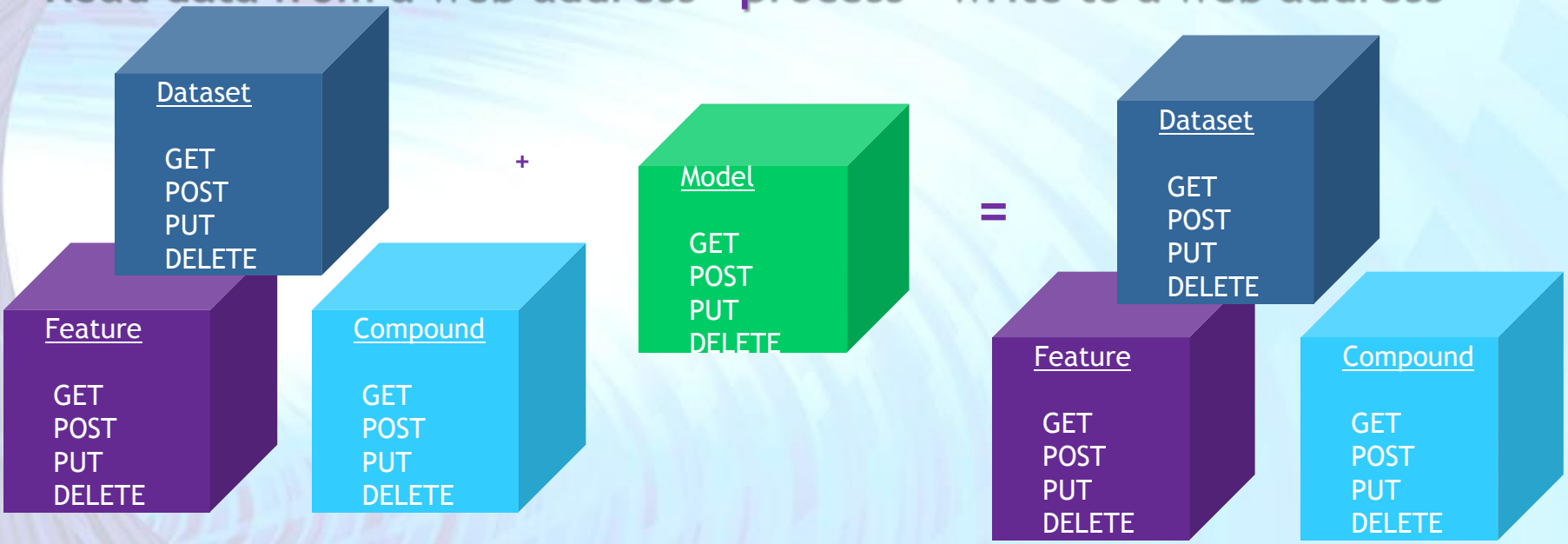
Uniform approach to model prediction

Read data from a web address - process - write to a web address

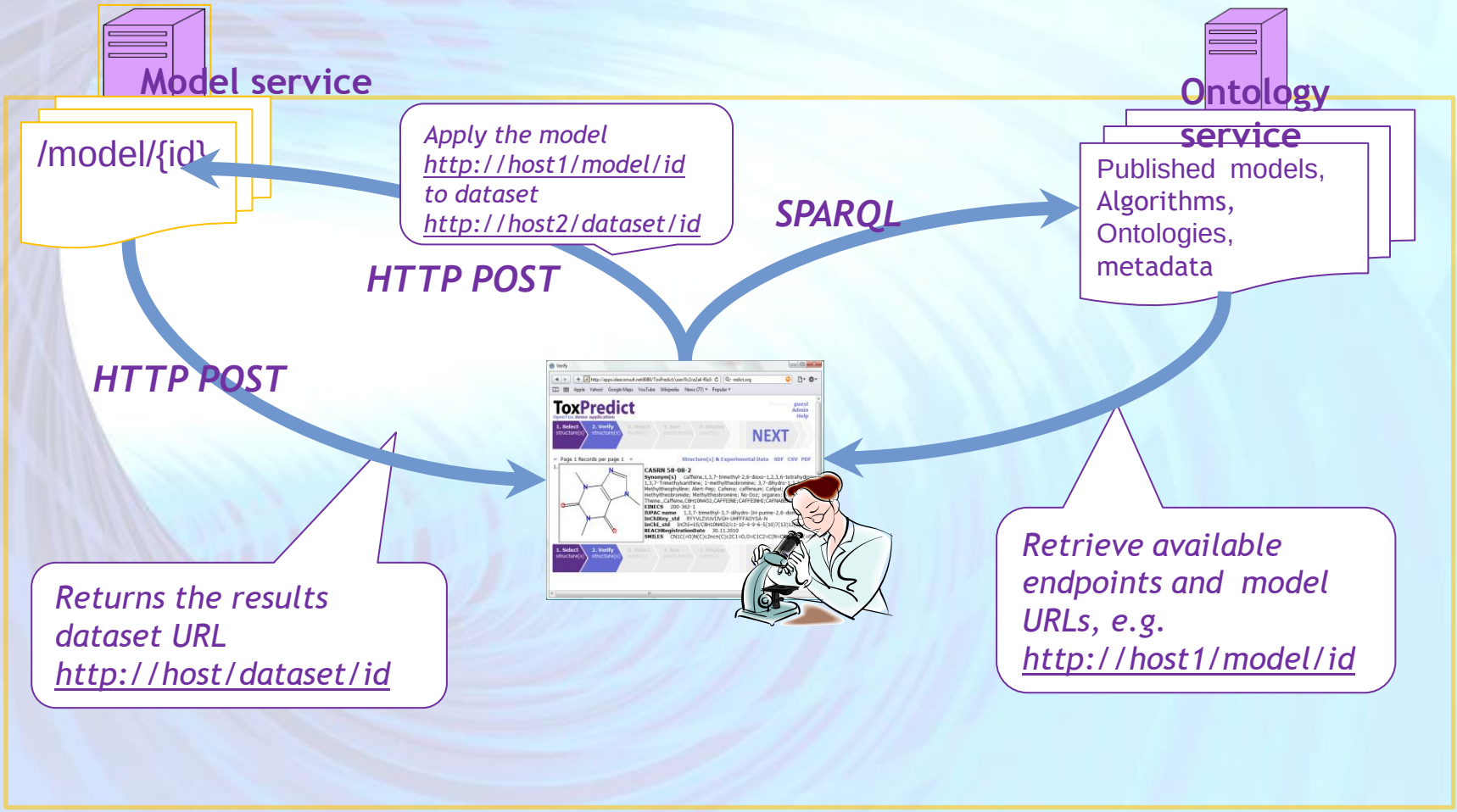


http://myhost.com/model/predictivemodel1

http://myhost.com/dataset/id1

http://myhost.com/dataset/results1

Apply predictive models



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Validation

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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Goodness-of-fit, robustness and predictivity

- OpenTox is developing unified and objective validation routines for model and algorithm developers and for external (Q)SAR programs, including procedures for validation with artificial test sets
  - (e.g. n-fold cross-validation, leave-one-out, simple training/test set splits, bootstrapping, Y-scrambling).
  - Validation services are completely independent of algorithm and model services
- An important goal is to integrate
  - statistical tests for the comparison of (Q)SAR models under consideration,
  - a versioned database to store validation results and their history,
  - and tools for the inspection of the toxicological plausibility of (Q)SAR predictions.

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Implemented validation algorithms

Classification methods

- Number of correctly classified instances
- Number of incorrectly classified instances
- weighted_area_under_roc
- f_measure
- num_false_positives, negatives
- num_true_positives, negatives
- sensitivity
- specificity
- Classification confusion matrix

Regression methods

- root_mean_squared_error
- mean_absolute_error
- sum_squared_error
- r_square
- correlation_coefficient

http://www.opentox.org/data/documents/development/validation/validation-statistics

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Uniform approach to models validation and report generation

Read data from a web address - process - write to a web address

http://myhost.com/dataset/trainingset1

http://myhost.com/dataset/predictedresults1

Validation report

http://myhost.com/validation

Validation

GET
POST
PUT
DELETE

+

Dataset

GET
POST
PUT
DELETE

=

Report

GET
POST
PUT
DELETE

Model generating predictions

Model

GET
POST
PUT
DELETE

http://myhost.com/report/1

http://myhost.com/model/predictivemodel1

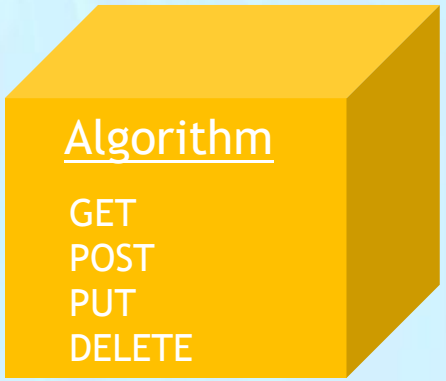
Applicability domain algorithms

A. The predictive model itself provides estimation of applicability domain

- Lazar

B. Applicability domain is estimated by a procedure , separate from the predictive model

- PCA ranges
- Euclidean distance
- Cityblock distance
- Mahalanobis distance
- Nonparametric density estimation
- Leverage
- Fingerprints, Tanimoto distance



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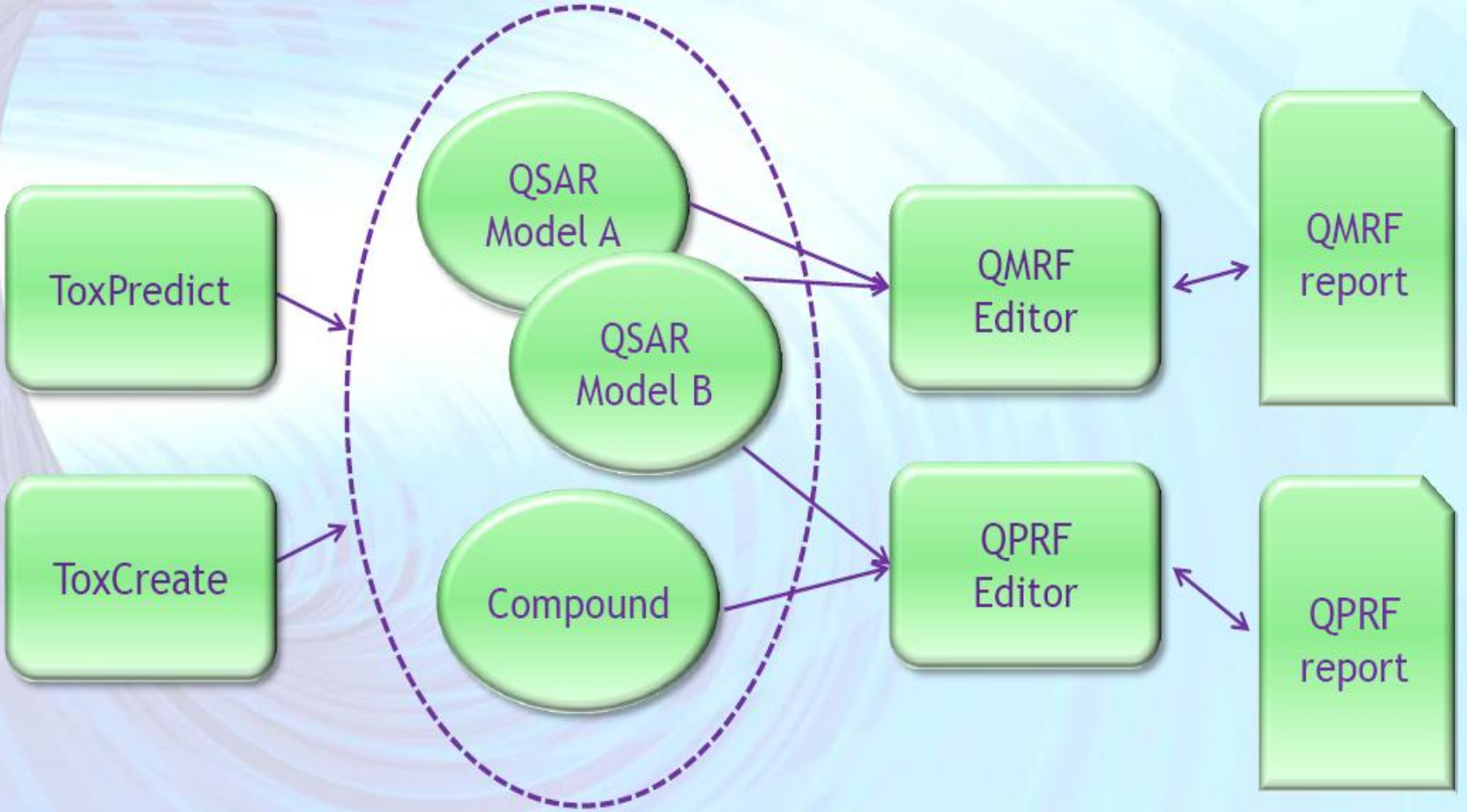
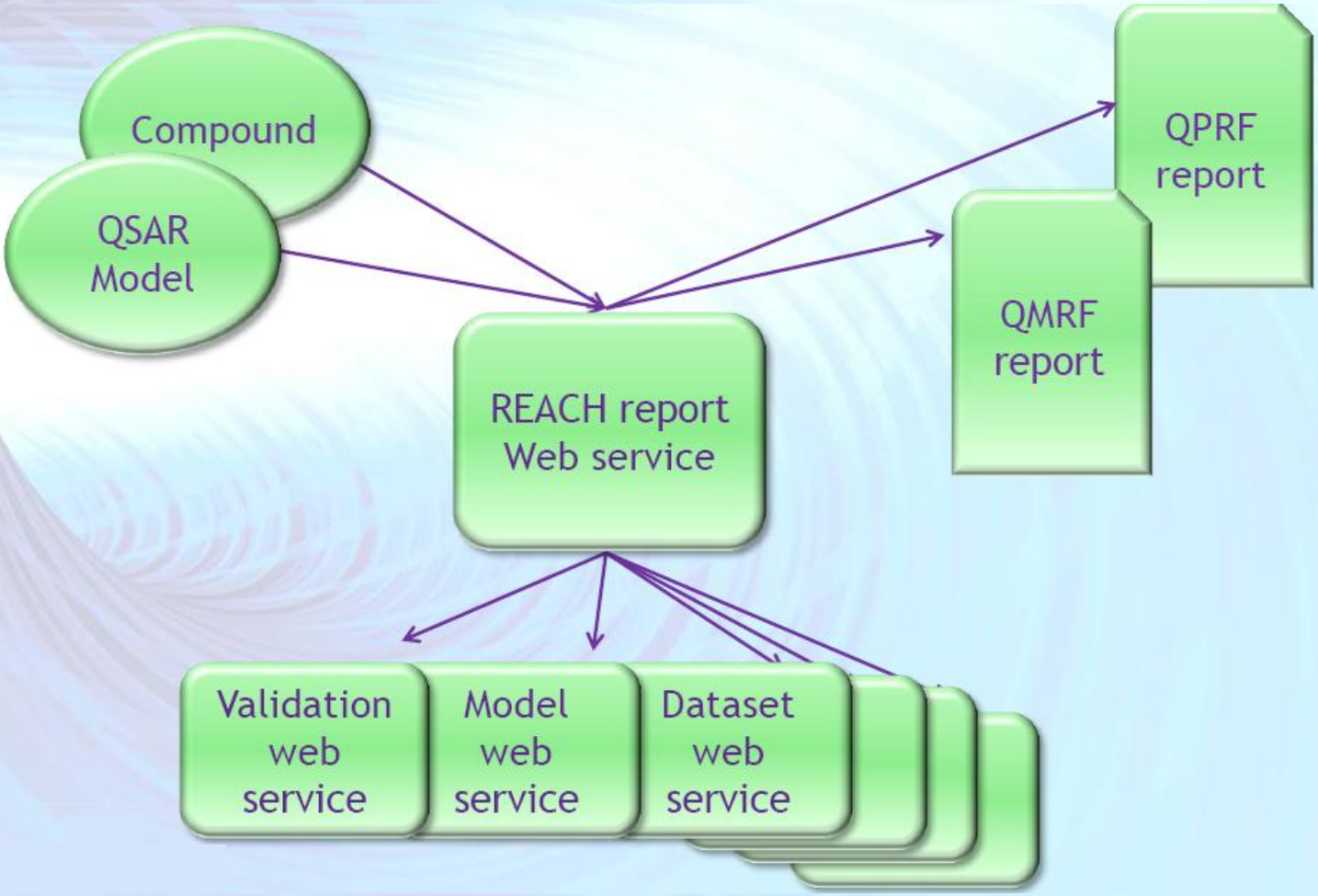
Reporting

- QMRF and QPRF
  - What are they?
    - Harmonized templates for summarizing and reporting key information on (Q)SAR models and predictions, generated by these models
  - Why it is important in OpenTox?
    - QMRF and QPRF are expected to be the communication tool between industry and the authorities under REACH

User perspective



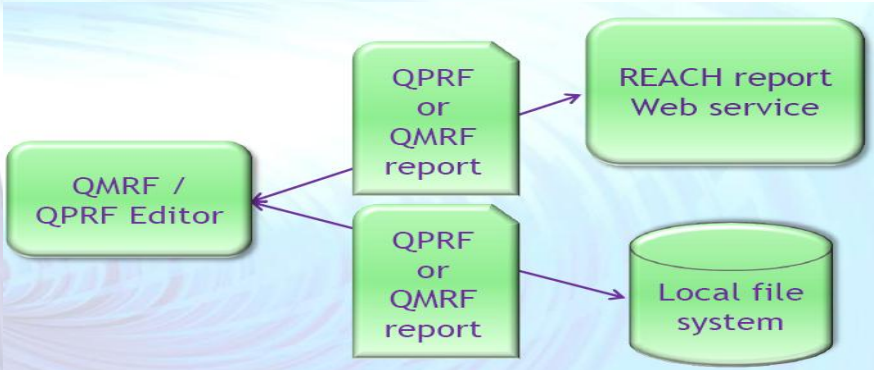
Creating reports

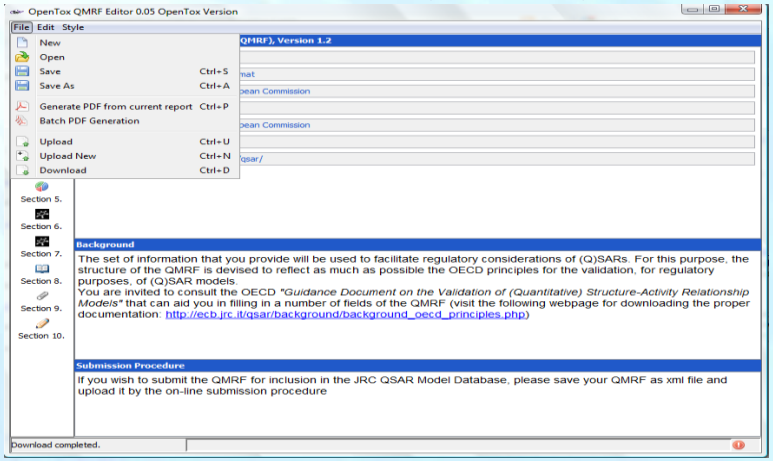


Storing and editing reports

1) QMRF editor OpenTox version

By Albert-Ludwigs-Universitat-Freiburg (ALU-FR) Germany





- Automatically populate relevant fields based on information , available in (distributed) algorithm , model, data, validation and reporting services
- Users can edit to add missing information
- Reports can be downloaded , uploaded, deleted from/to OpenTox reporting service

2) QPRF editor (Q-Edit)

http://opentox.ntua.gr/Q-edit/dist/launch.jnlp

Live demo by Pantelis Sopasakis,

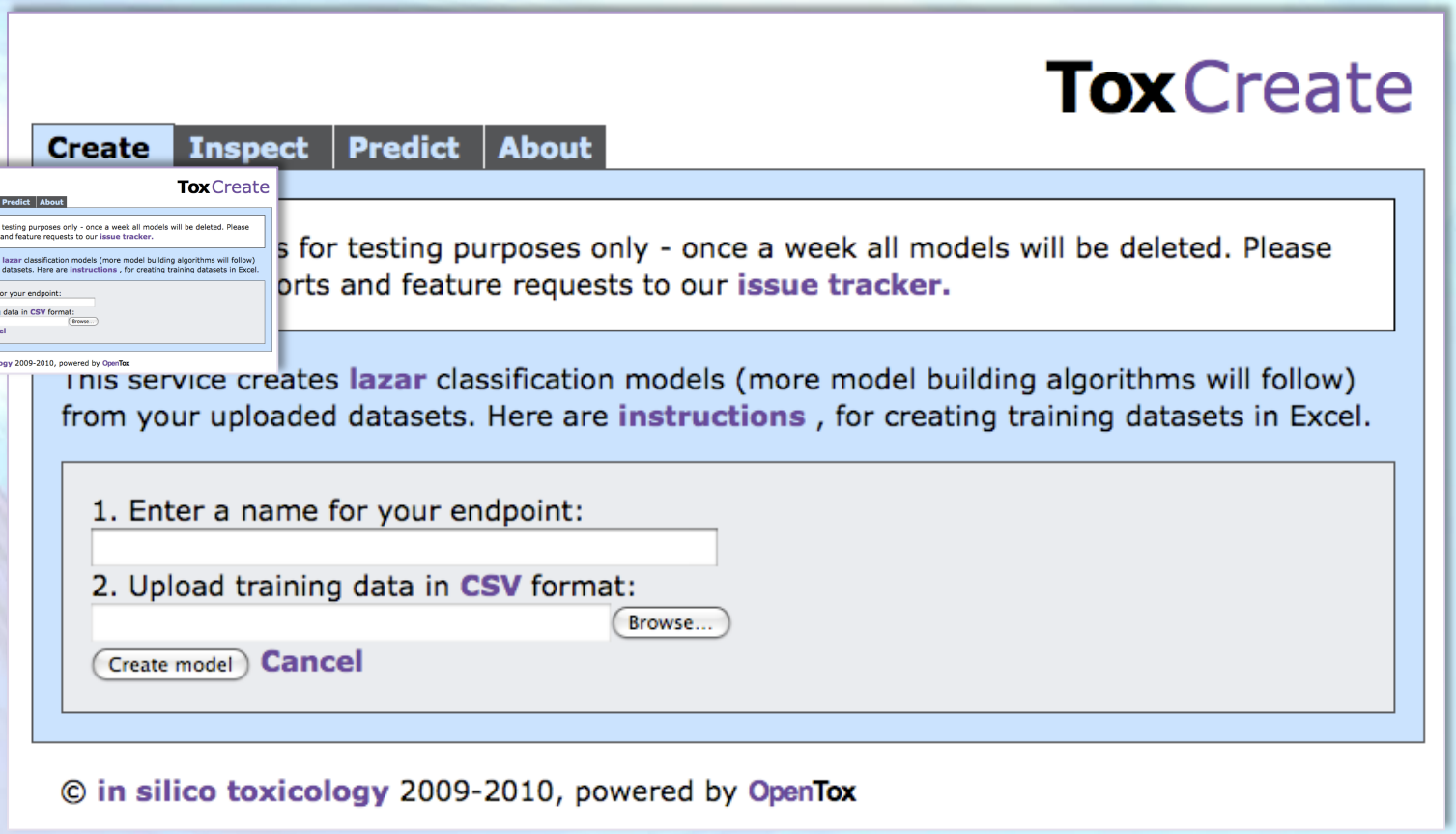
National Technical University of Athens

What can you do with OpenTox

- Build simple applications, based on existing algorithms , methods and data
- Distributed applications, integrating wide range of data and methods
- Examples:
  - ToxCreate (web application), ToxPredict (web application), QMRFEditor (Java web start), QPRF Editor (Java web start)
  - More under development

ToxCreate http://toxcreate.org

ToxCreate creates models from user supplied datasets. Developed and hosted by IST (Christoph Helma).
Uses OpenTox algorithm, model, compound, dataset and validation services



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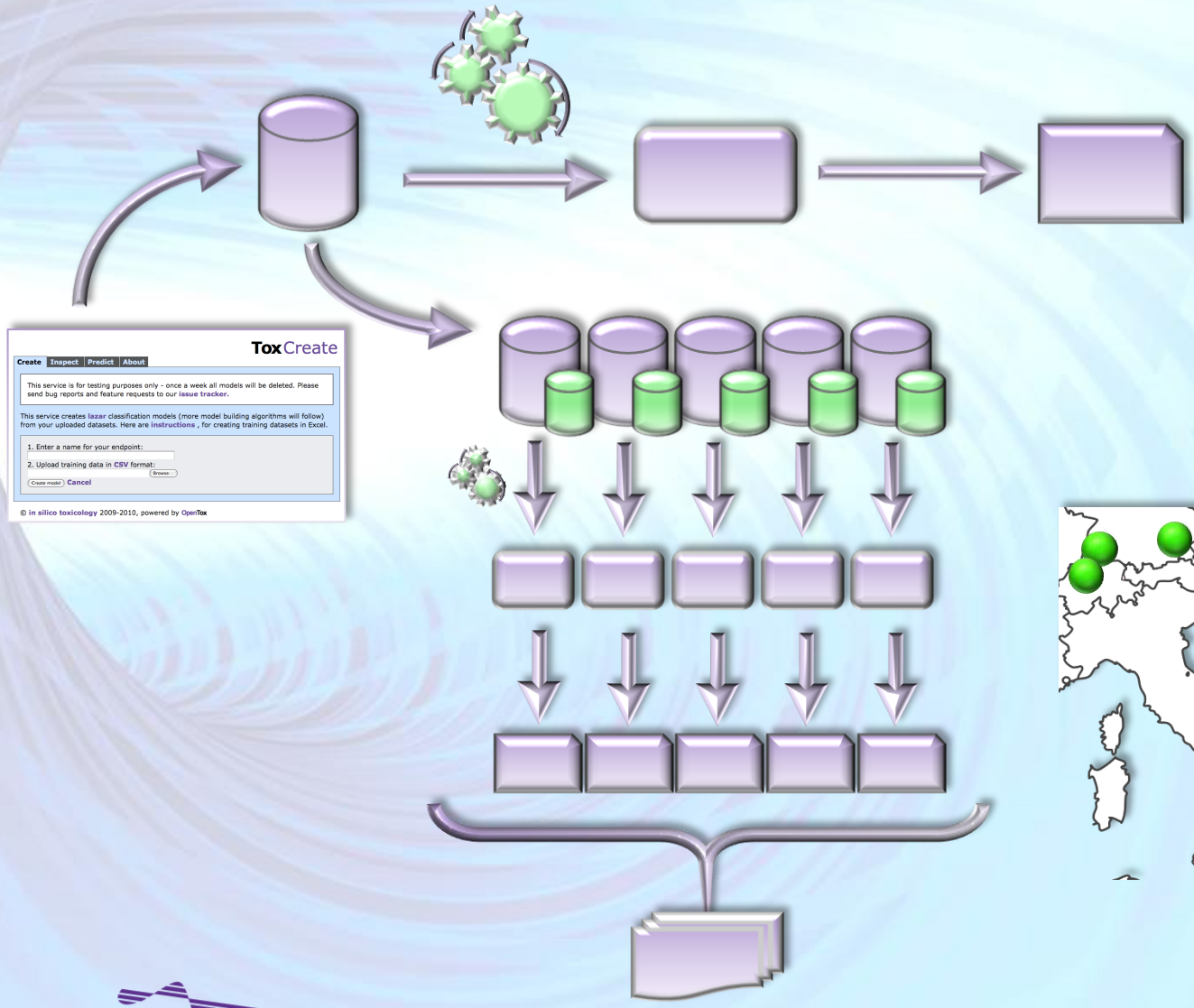
ToxCreate (behind the scenes)



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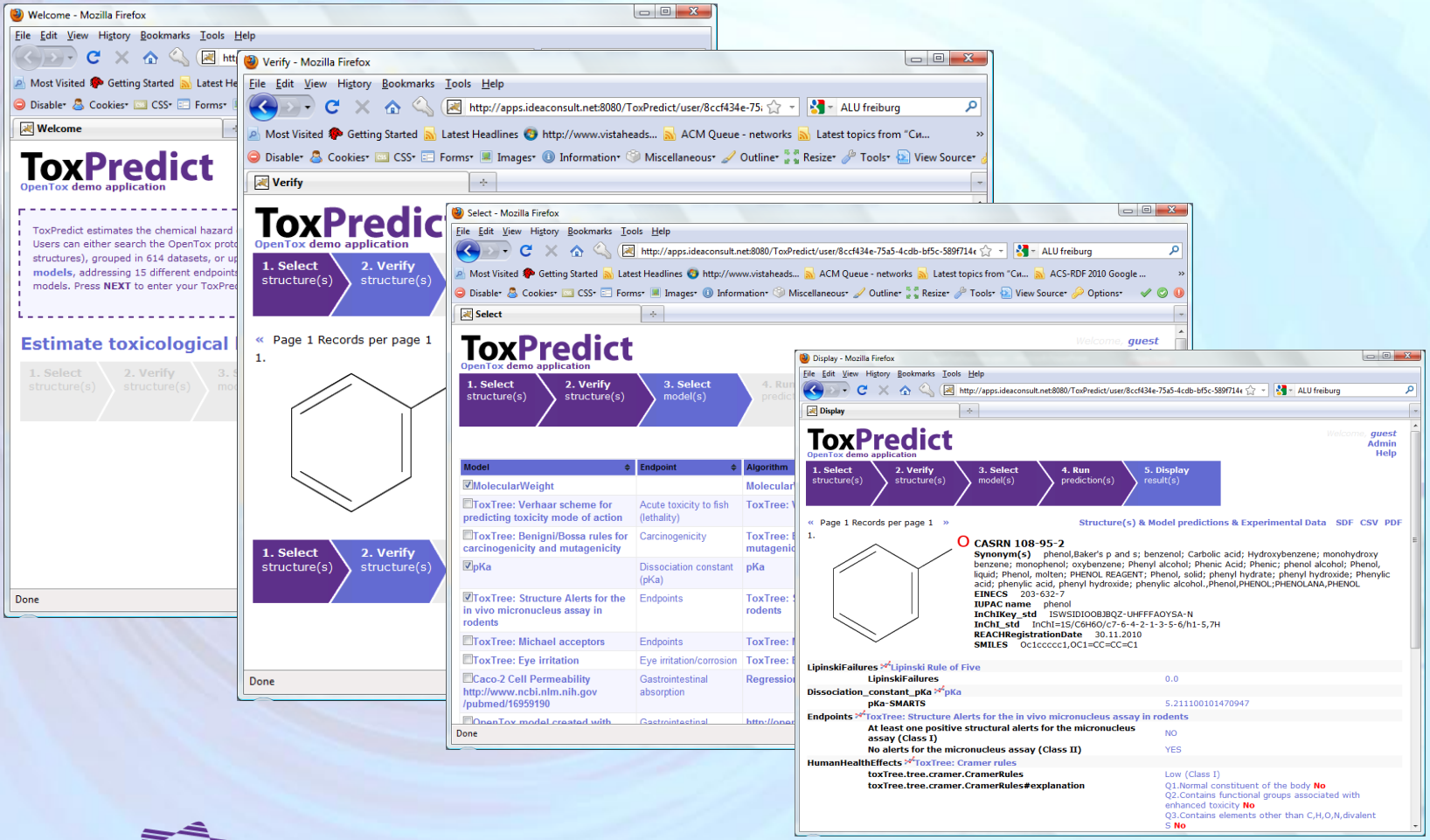
ToxPredict http://toxpredict.org

ToxPredict uses existing OpenTox models to estimate chemical compound properties. Developed and hosted by IdeaConsult.



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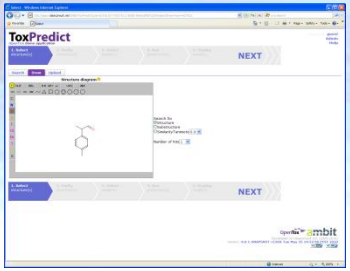
ToxPredict (behind the scenes)



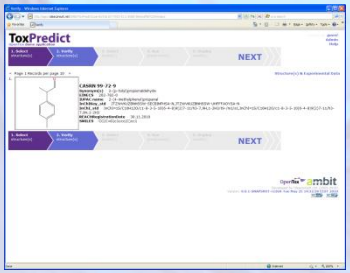
Find structure by name, registry number, SMILES, InChI, structure, substructure, similarity…

ToxPredict Web Application

OT Dataset API ***HTTP GET***

OT Dataset Service

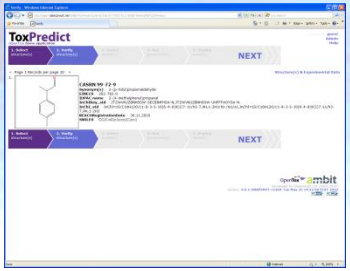
text/uri-list,
application/rdf+xml,
chemical/x-daylight-smiles
chemical/x-mdl-sdfile,…



Here is the list of structures as URI links, RDF, MOL or SMILES.

OpenTox

ToxPredict (behind the scenes)



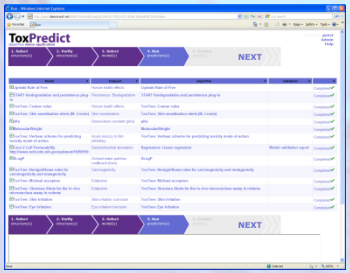
What prediction models are available? Is there a model for endpoint X?

ToxPredict Web Application

HTTP GET SPARQL query

OT Ontology Service

application/sparql-results+xml



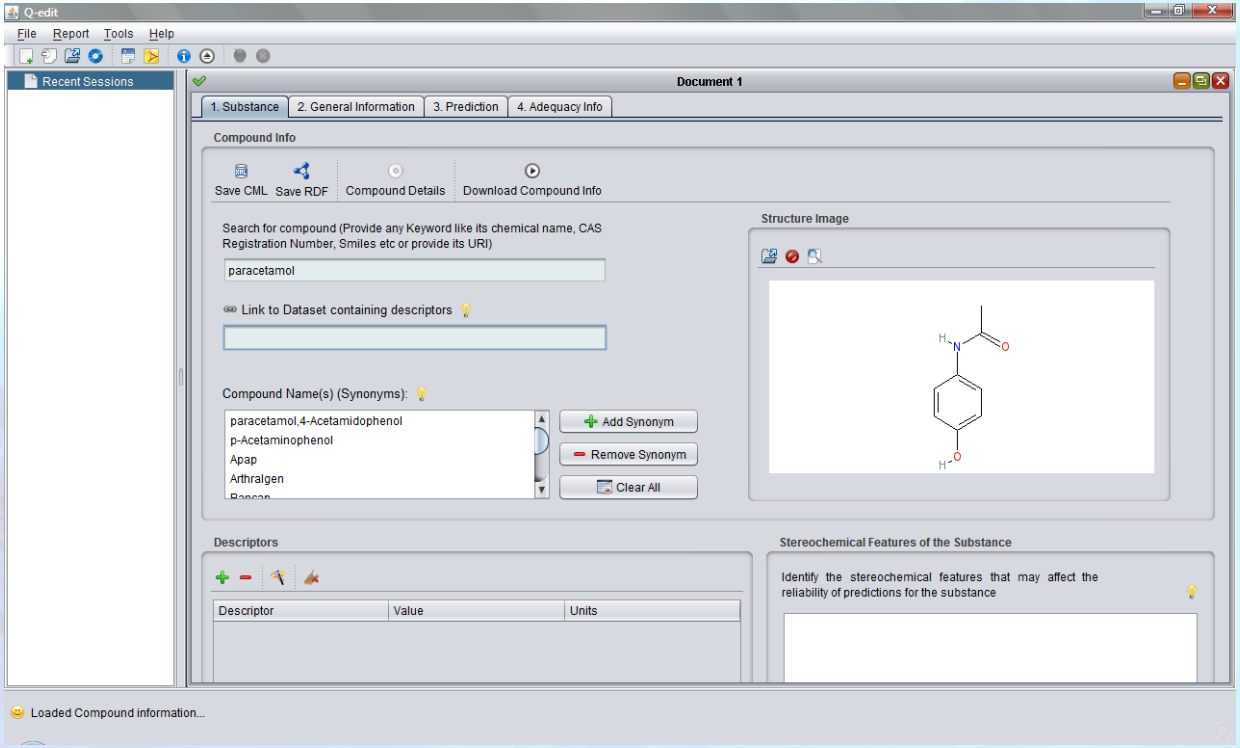
Here is the list of model URIs and related endpoints and algorithms in SPARQL format.

OpenTox

Q-Edit demo

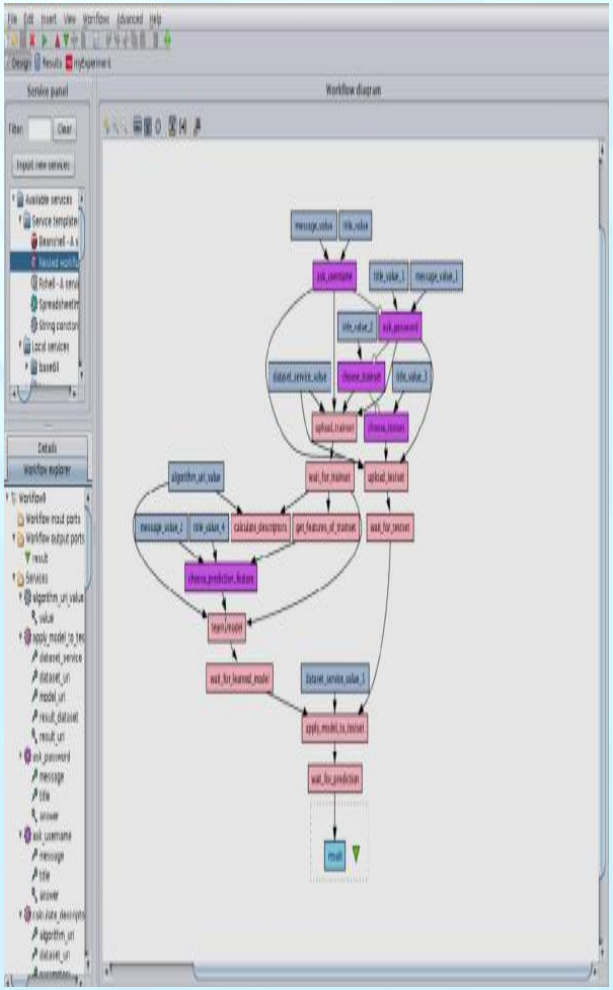
http://opentox.ntua.gr/Q-edit/dist/launch.jnlp

Q-Edit uses existing OpenTox models and data services to create QPRF report. Developed and hosted by NTUA.

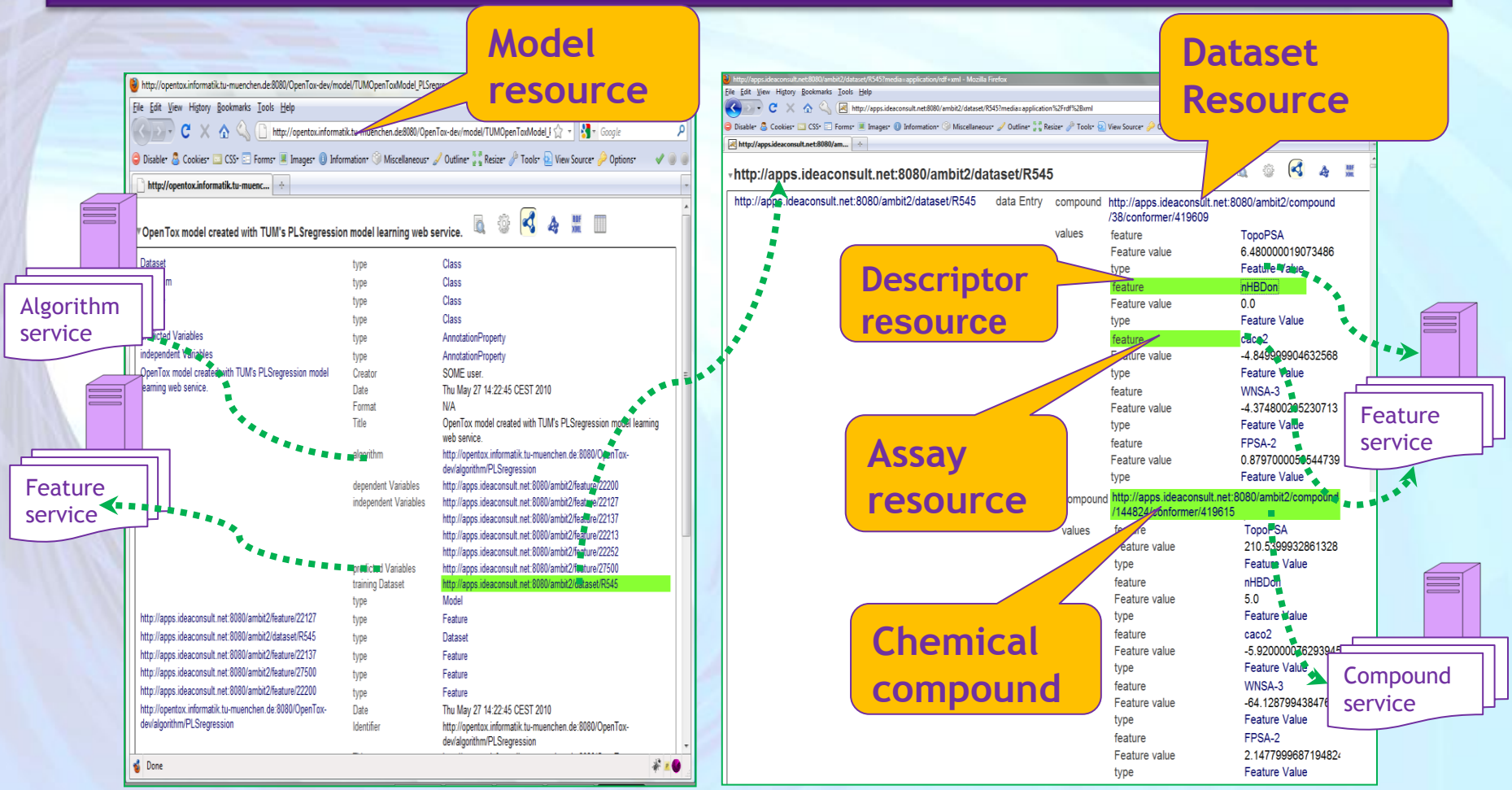


What can you do with OpenTox

- Integration into
  - Workflow systems : Taverna, Knime, Pipeline Pilot
  - Applications : Bioclipse
- Run your own instances of (subset) OpenTox services
  - Expose your new predictive algorithm as OpenTox algorithm or model service
  - Publish your data as OpenTox dataset
- Query ontology services to find out
  - datasets or models (possible remote)
  - for particular endpoint, type of algorithm, etc.



Linked resources: Compound, Algorithm, Model, Dataset, Features



Summary

- OpenTox is a framework for predictive toxicology
- Designed for language independence, transparency and extensibility
- Implemented as open source REST web services
- Exchange of data and knowledge with ontologies (RDF, OWL-DL)
- OpenTox components: Compound, Feature, Dataset, Algorithm, Model, Validation, Report, Task, Authentication and Authorisation
- Documentation: www.opentox.org/dev

Thank you!

EC FP7 CADASTER
http://www.cadaster.eu

EC FP7 OpenTox
http://www.opentox.org