6th FIP 19/22 Pharmaceutical Sciences World Congress (PSWC)

Stockholm, Sweden
21-24 May 2017

The eTOX project: pooling legacy data to advance safety sciences

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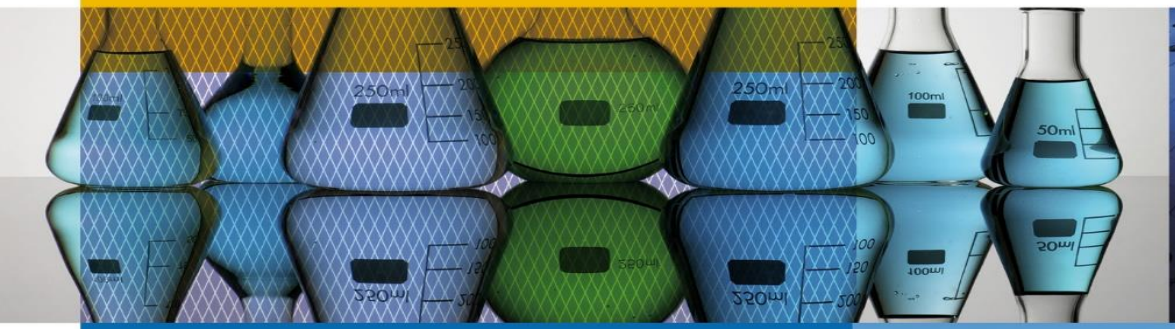
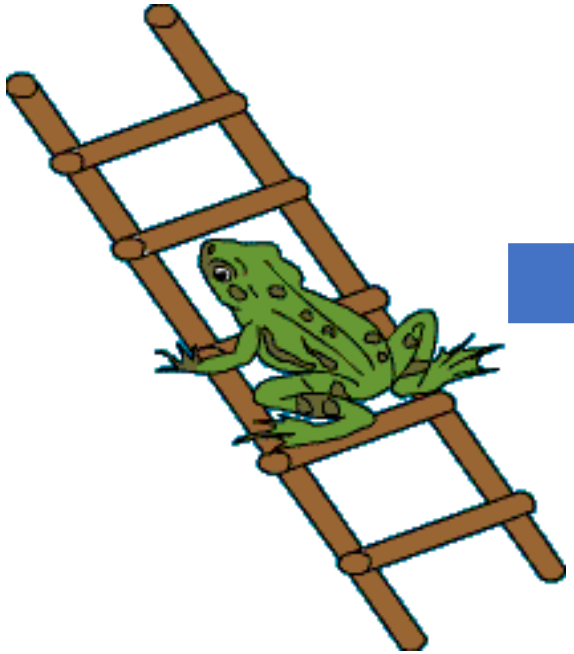


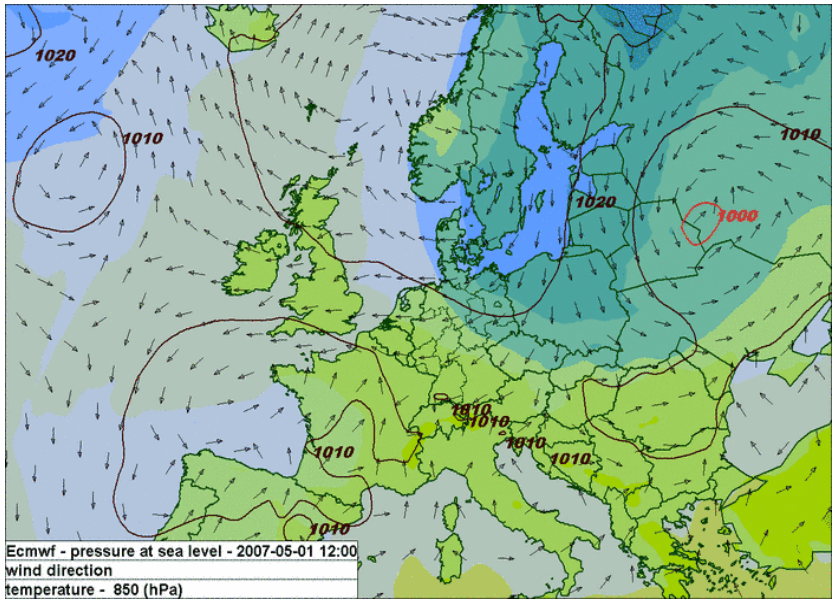
fip STOCKHOLM PSWC 21-24 May 2017

Weather forecast

In the past



Nowadays

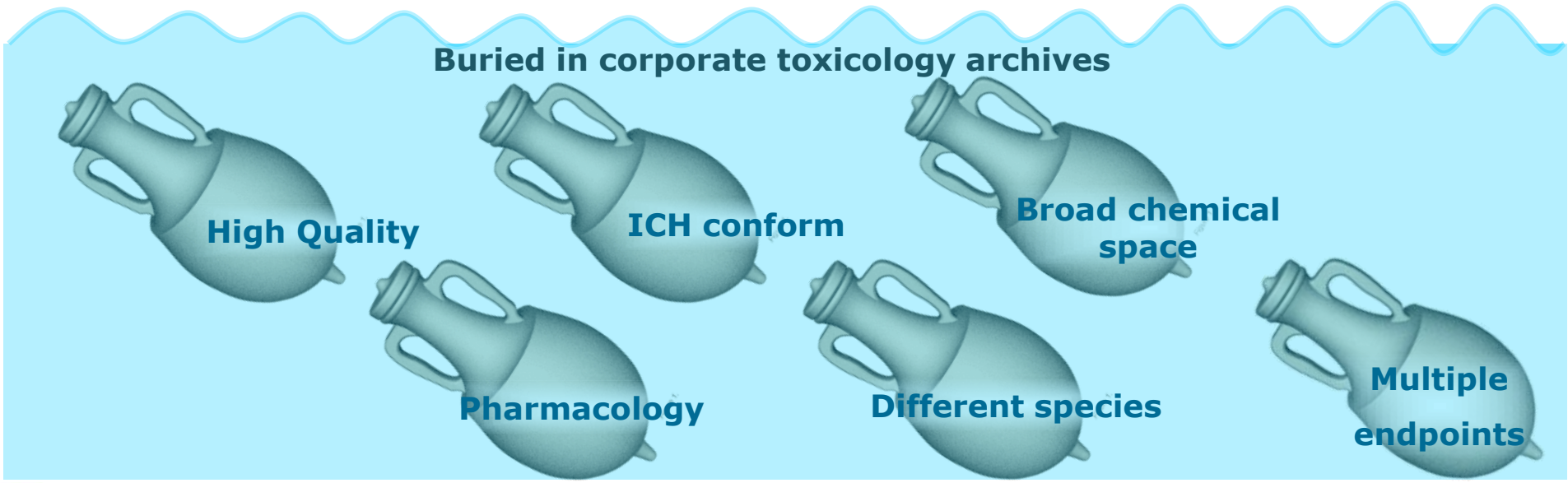


Current computational sciences allows the development of reliable predictive systems on the basis of considering a wide and relevant scope of previous information

Opportunity for better drug safety predictions

The wealth of the high quality toxicology data in the archives of the pharmaceutical companies was not yet leveraged.

efpia



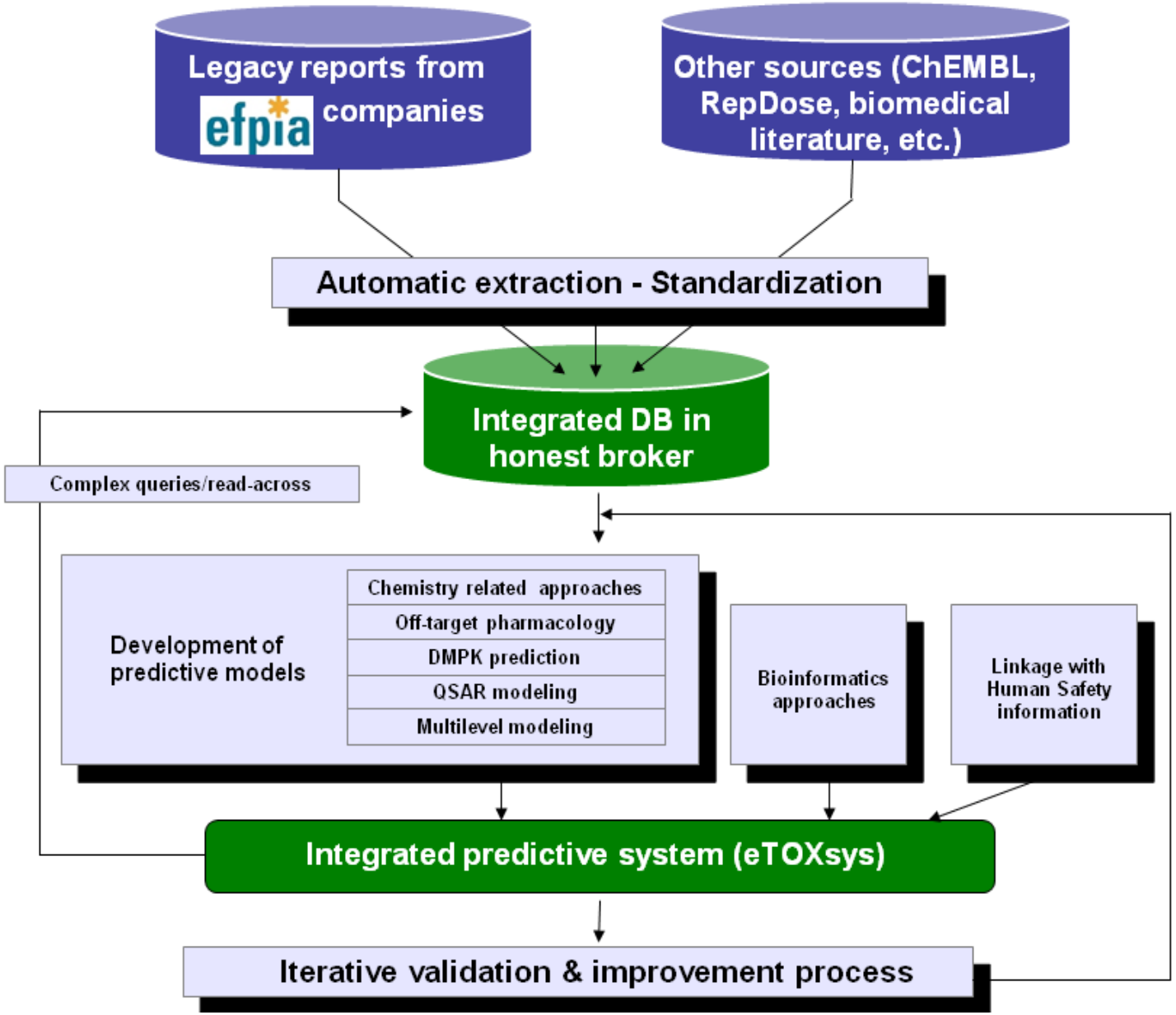
eTOX efpia imi innovative medicines initiative

Int. J. Mol. Sci. **2014**, *15*, 21136-21154; doi:10.3390/ijms151121136

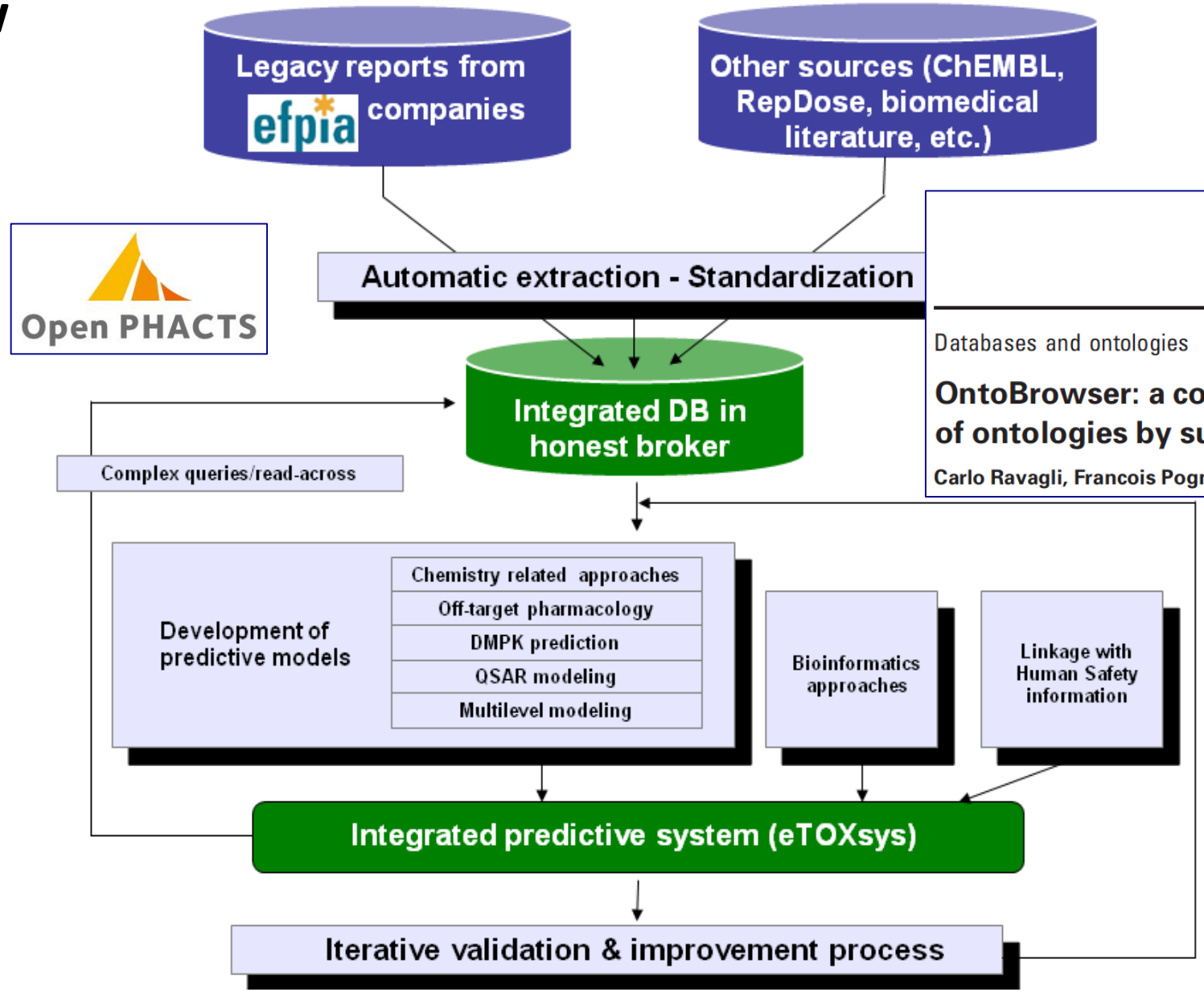
The eTOX Data-Sharing Project to Advance *in Silico* Drug-Induced Toxicity Prediction

- **IMI project** from its 1st call
- Total budget: **18.7 M€**
- EC funding: **6.9 M€**
- In kind contribution from EFPIA companies: **10.1 M€**
- Duration: **5 years + 2 years** ENSO extension *(from 1/2010 till 12/2016)*
- **13 EFPIA companies**: Novartis, Bayer, AstraZeneca, Boehringer, Esteve, GSK, Janssen, Lundbeck, Pfizer, Roche, Sanofi-Aventis, Servier, UCB.
- **11 academic institutions**: FIMIM, Danish Technical University, EBI, Erasmus Medical Center, ISCIII, ITEM, Universities of Leicester, Liverpool and Vienna, Free University of Amsterdam, Polytechnic University of Valencia.
- **6 SMEs**: Chemotargets, Inte:Ligand, Lhasa, LMD, MN, Synapse

eTOX workflow



eTOX workflow



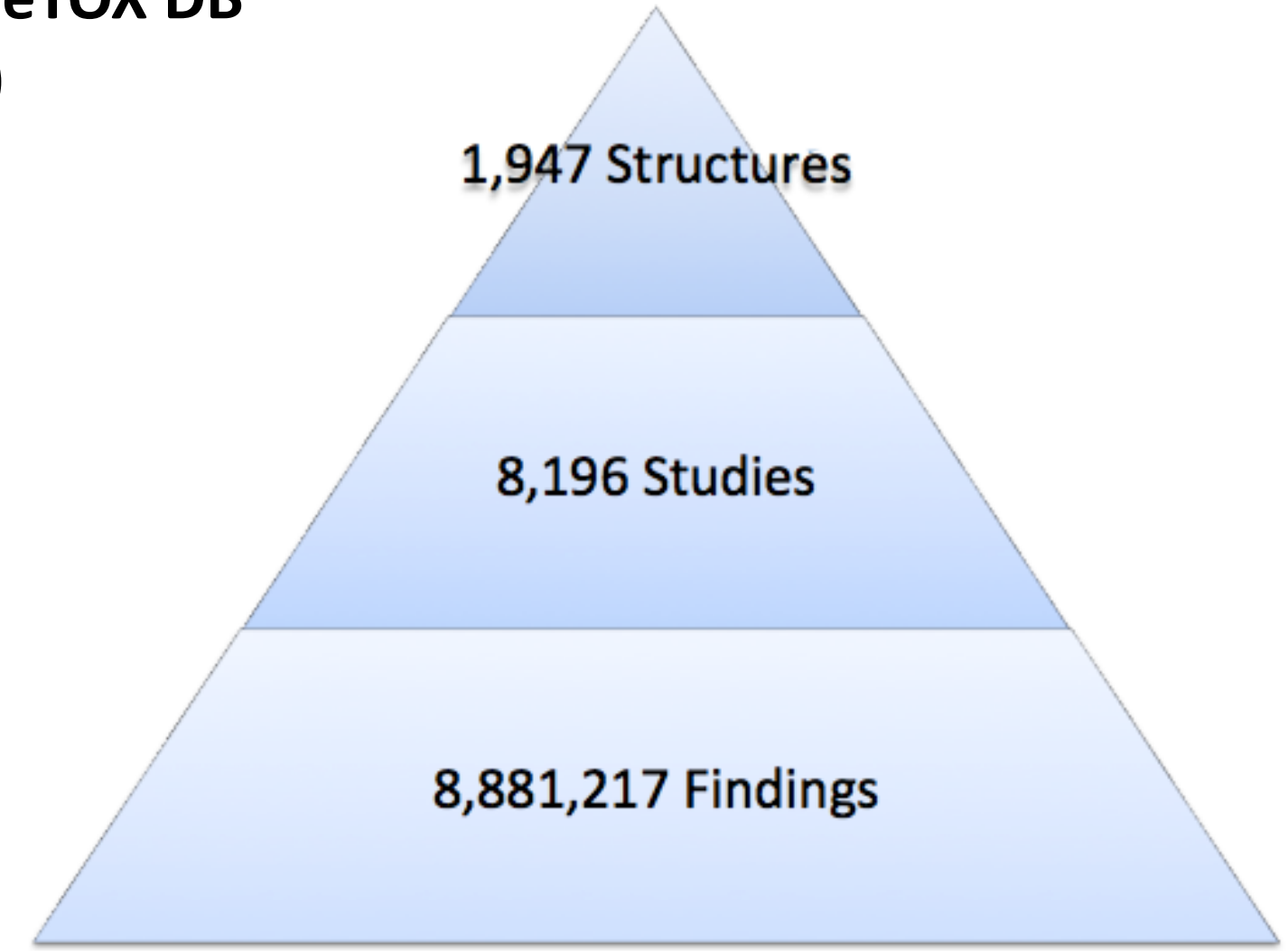
Bioinformatics, 33(1), 2017, 148–149
doi: 10.1093/bioinformatics/btw579
Advance Access Publication Date: 6 September 2016
Applications Note

Databases and ontologies

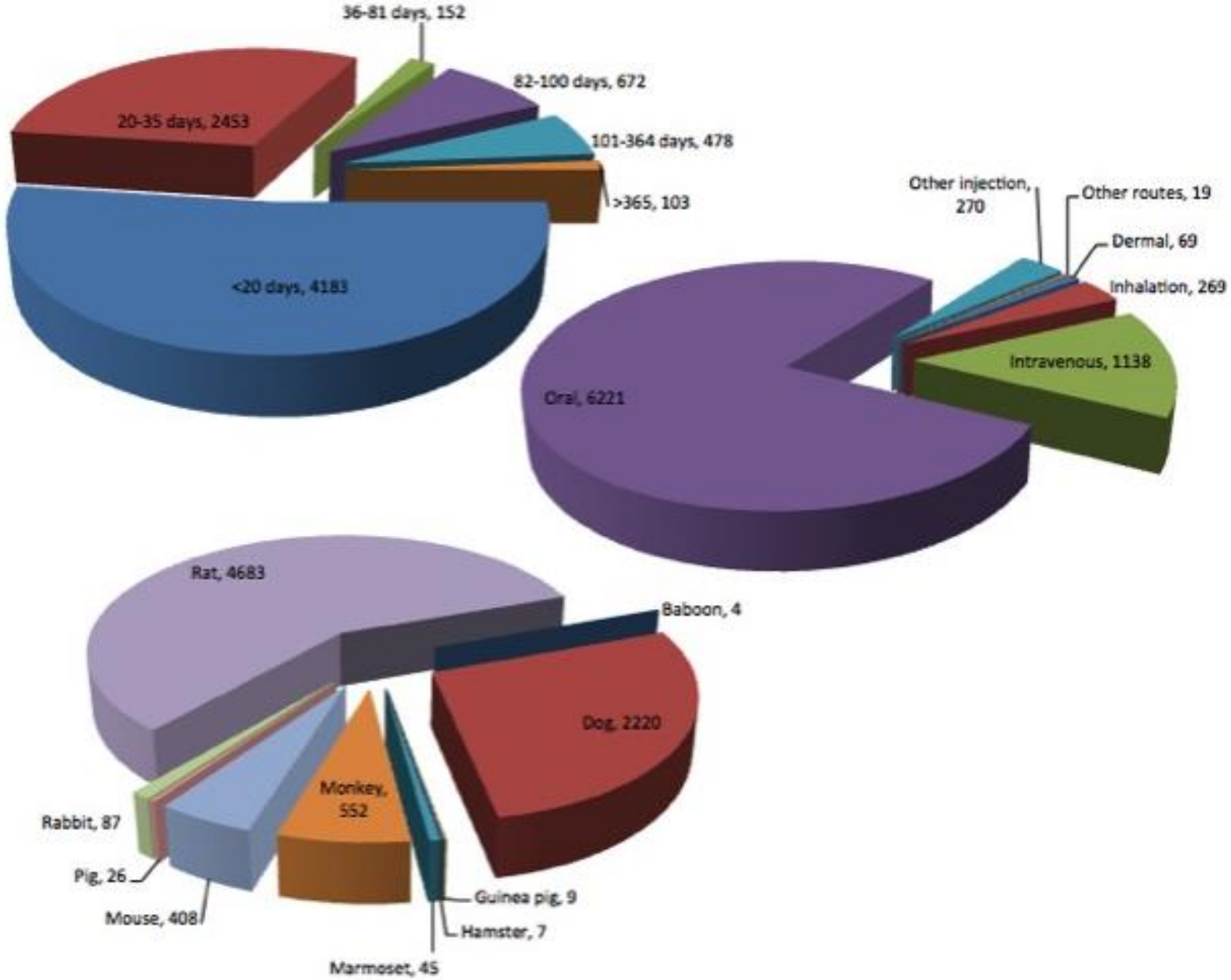
OntoBrowser: a collaborative tool for curation of ontologies by subject matter experts

Carlo Ravagli, Francois Pognan and Philippe Marc*

Contents of the eTOX DB (version 2016.3)



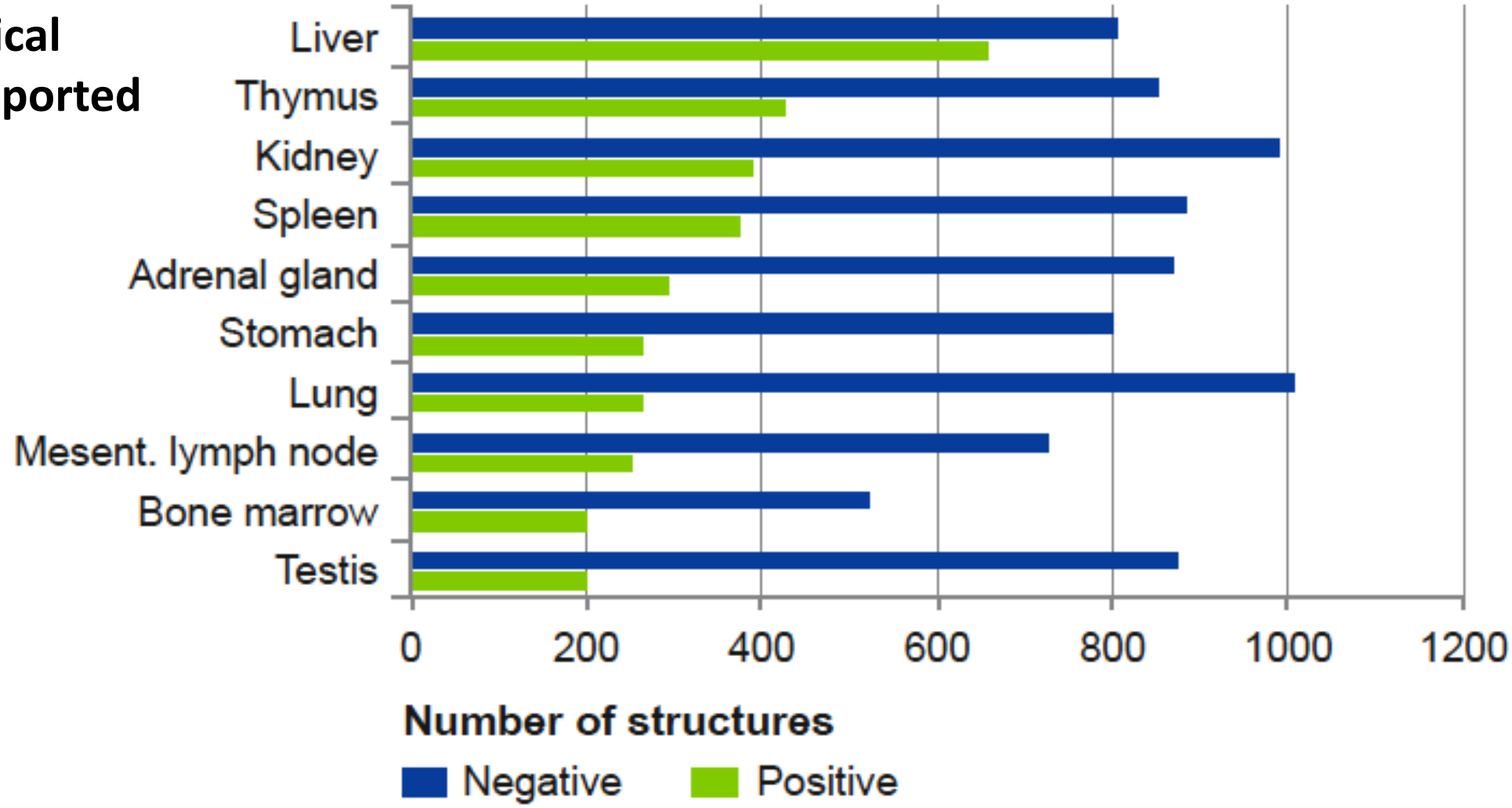
eTOX DB (version 2016.3): Breakdown by duration, administration route and duration



Ferran Sanz – GRIB (IMIM-UPF)

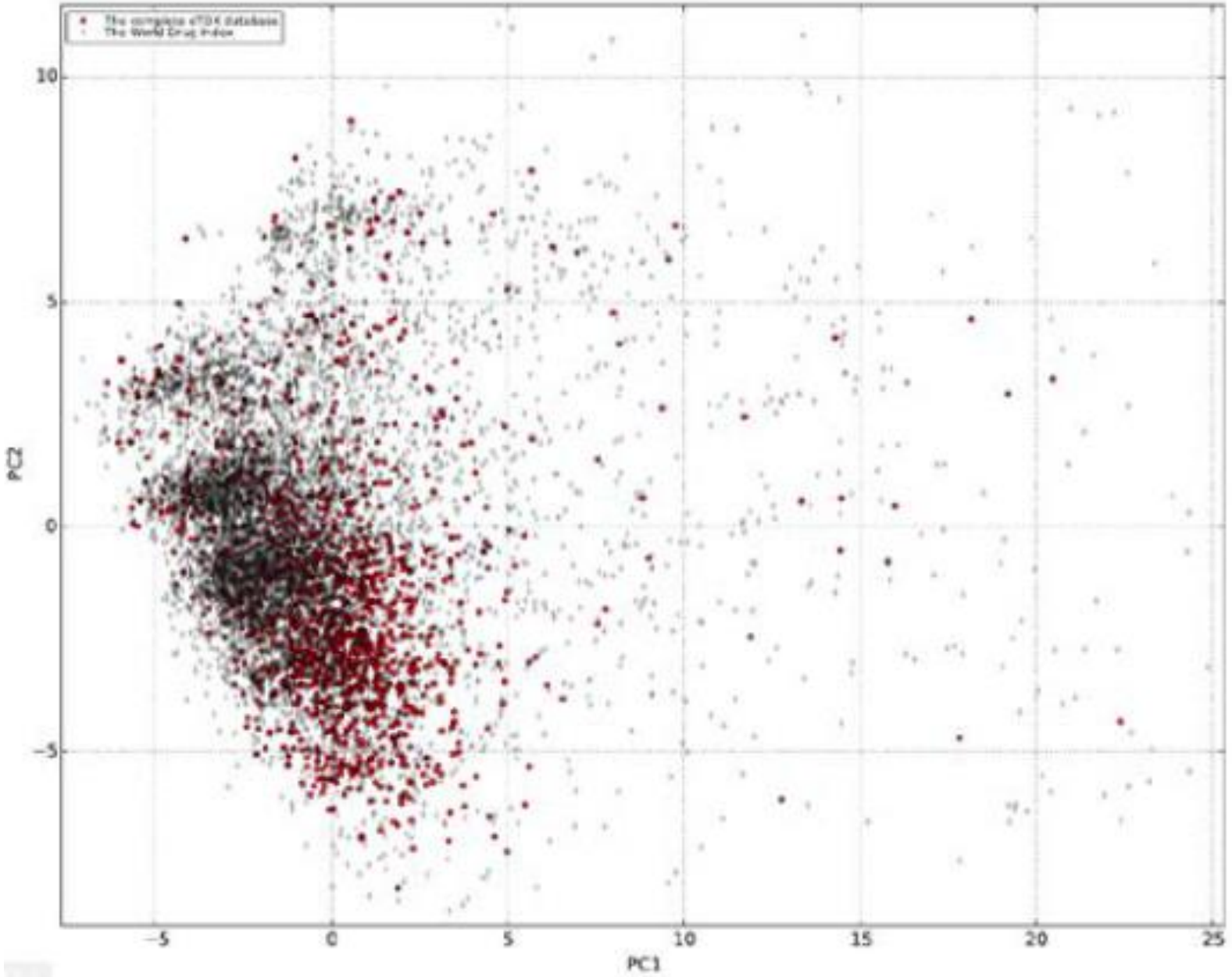
eTOX DB:

Most frequent organs for which toxicological findings were reported



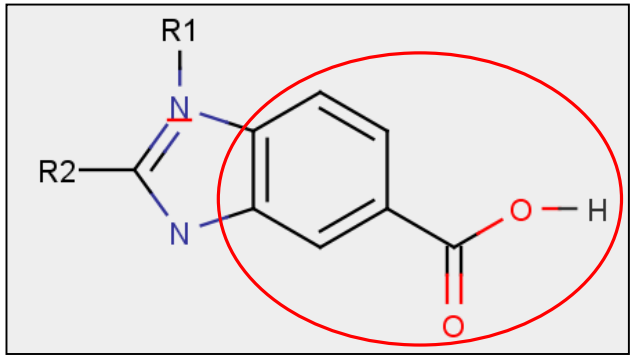
eTOX DB:
Chemical space coverage

- Drug World Index
- eTOX DB

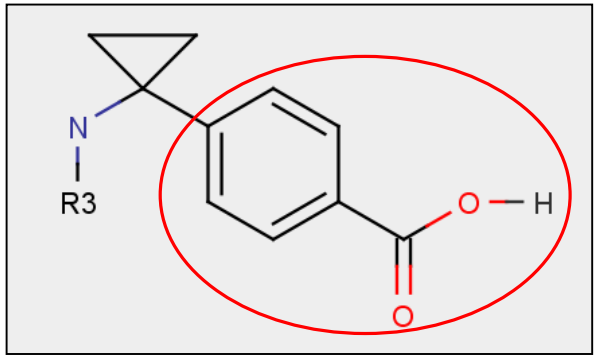


eTOX application example

An early Bayer drug candidate and a competitor compound share a common substructure:



Common Substructure (benzoic acid)



In rat toxicological studies the following common hematological findings were observed:

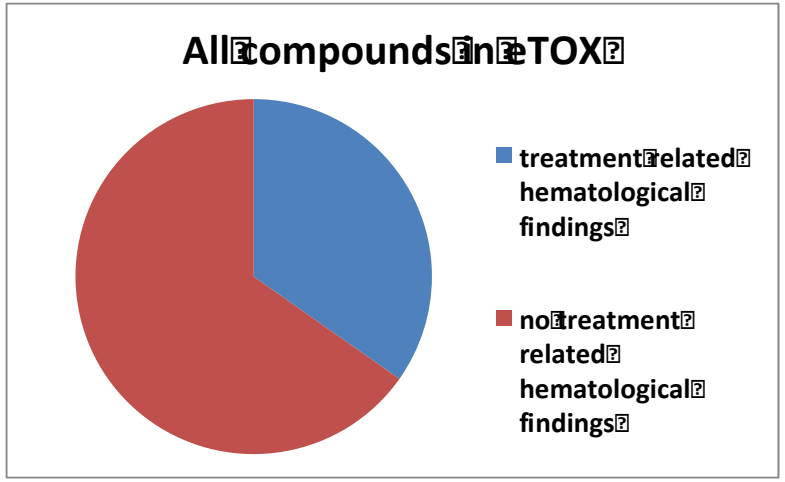
- Decrease in erythrocytes and hemoglobin
- Increase in reticulocytes
- Increase in thrombocytes
- Increase in leucocytes and neutrophils

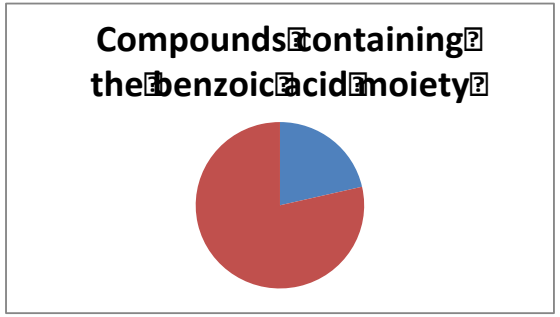
Are these hematological findings related to the chemical structure/substructure?

eTOX application example

Search in the eTOX DB:

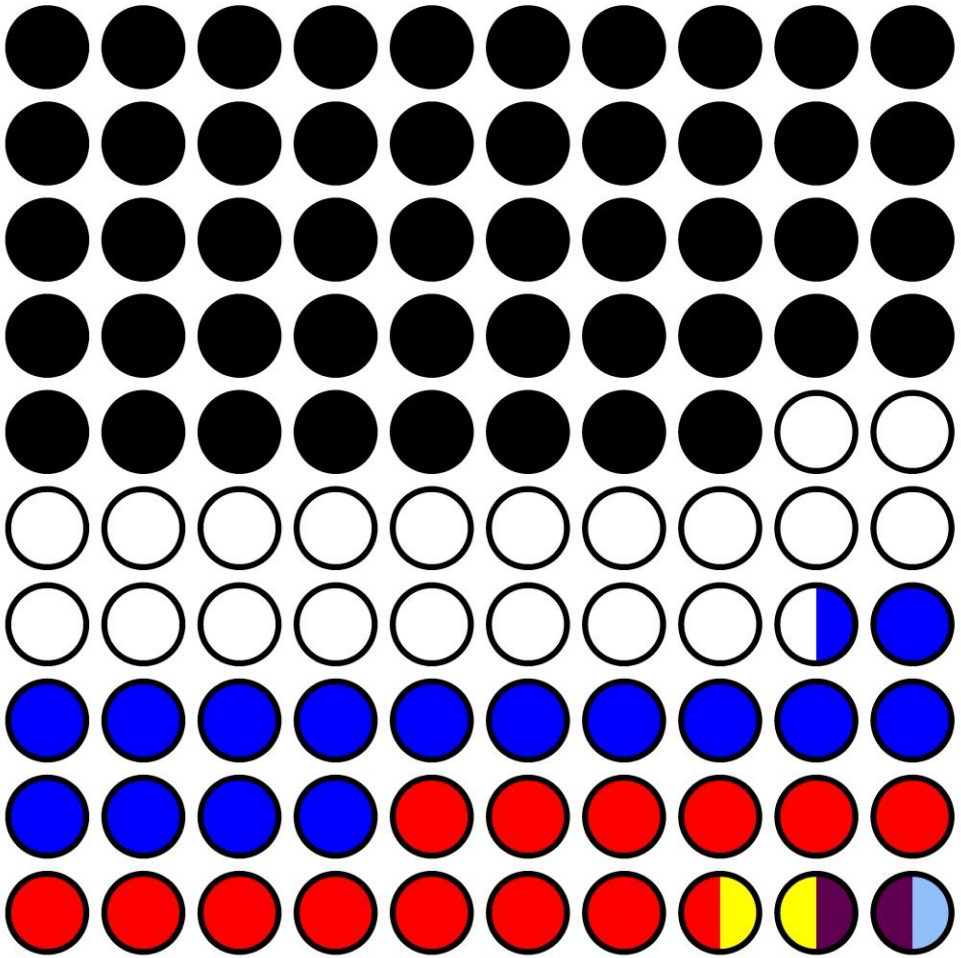
- ❑ 14 of 1248 compounds contain the benzoic acid moiety
- ❑ 3 of these 14 compounds have treatment related hematological findings (21%)
- ❑ 434 of the overall 1248 compounds have treatment related hematological findings (34%)





There was no evidence that the treatment-related hematological findings are over-represented in the group of compounds incorporating a benzoic acid moiety.

eTOX computational models



97 Target Safety Pharmacology
41 Organ toxicity
32 ADME
27 Transporters
2 Carcinogenicity
2 Genotoxicity
1 Phys.chem. properties

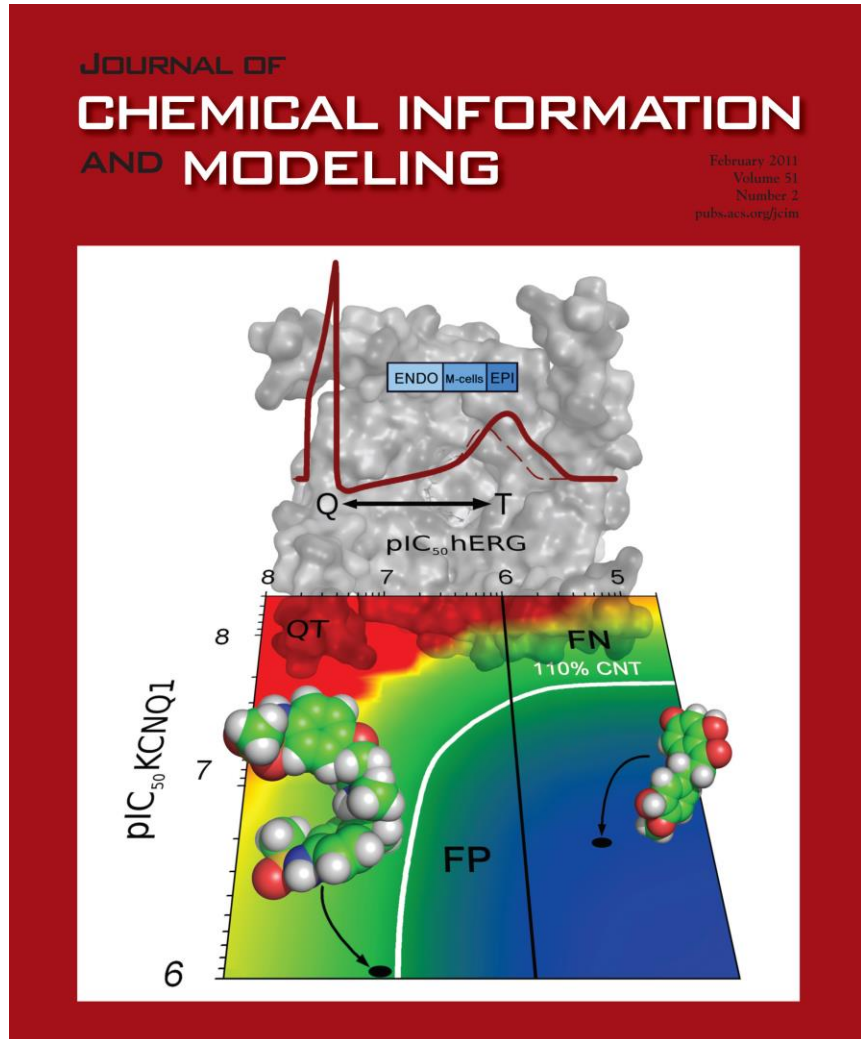
JOURNAL OF CHEMICAL INFORMATION AND MODELING

ARTICLE

pubs.acs.org/jcim

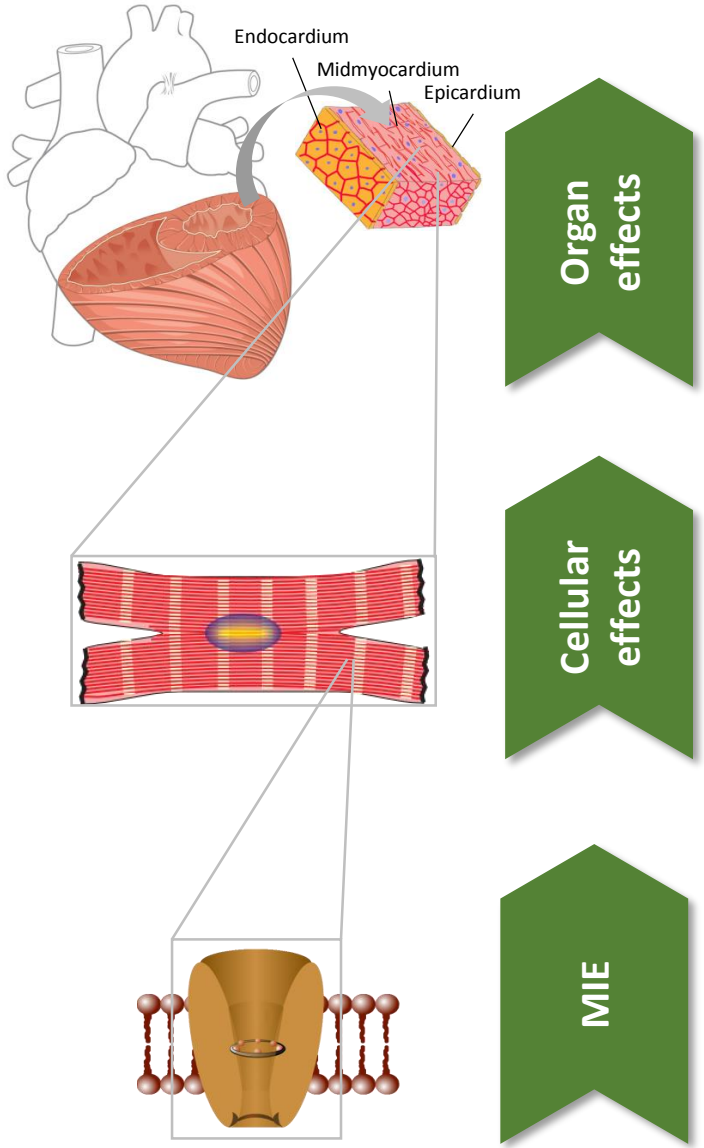
A Multiscale Simulation System for the Prediction of Drug-Induced Cardiotoxicity

Cristian Obiol-Pardo,[†] Julio Gomis-Tena,[‡] Ferran Sanz,[†] Javier Saiz,[‡] and Manuel Pastor*[,†]



J. Chem. Inf. Model. 2011, 51, 483–492

QT prolongation multi-scale model

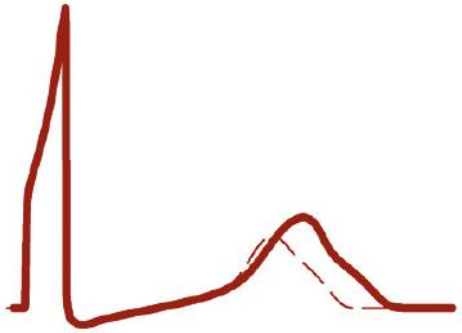


Effects on the transmission of the action potential in the ventricular tissue. Generation of a simulated ECG in which the QT prolongation can be observed

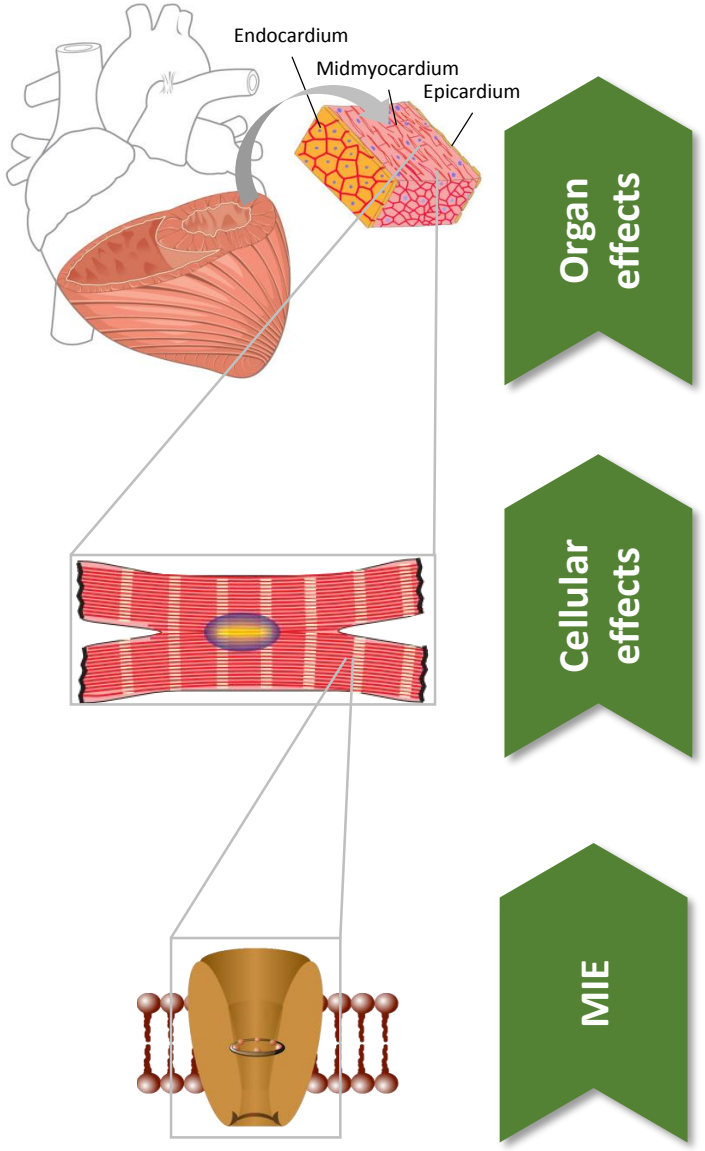
Disruption of K+, Na+ and Ca2+ currents and perturbation of the cardiomyocyte action potential

Blockade of key ion channels (e.g. hERG)

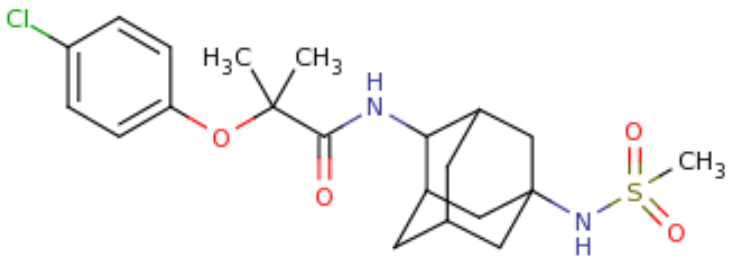
QT prolongation multi-scale model



The output is the possible ECG alteration



The input is the 2D structure of a possible drug

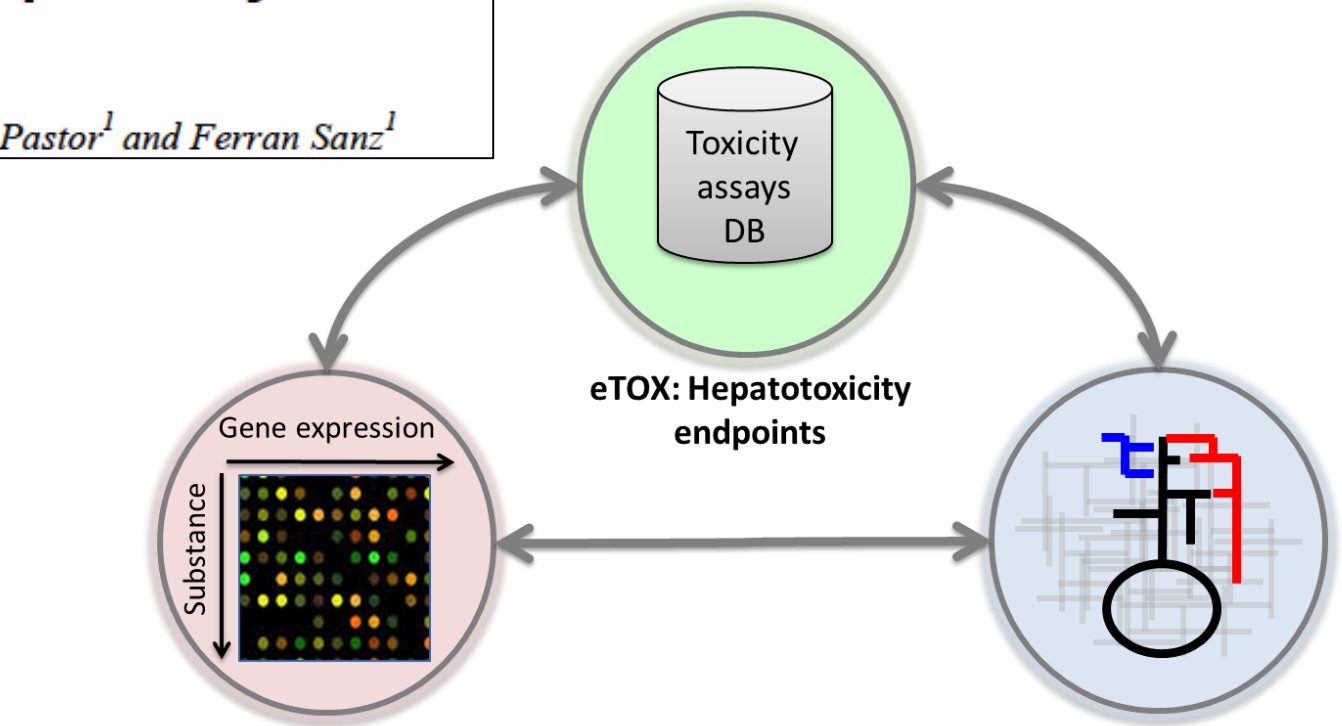


ALTEX Online first
published September 30, 2016
http://dx.doi.org/10.14573/altex.1602071

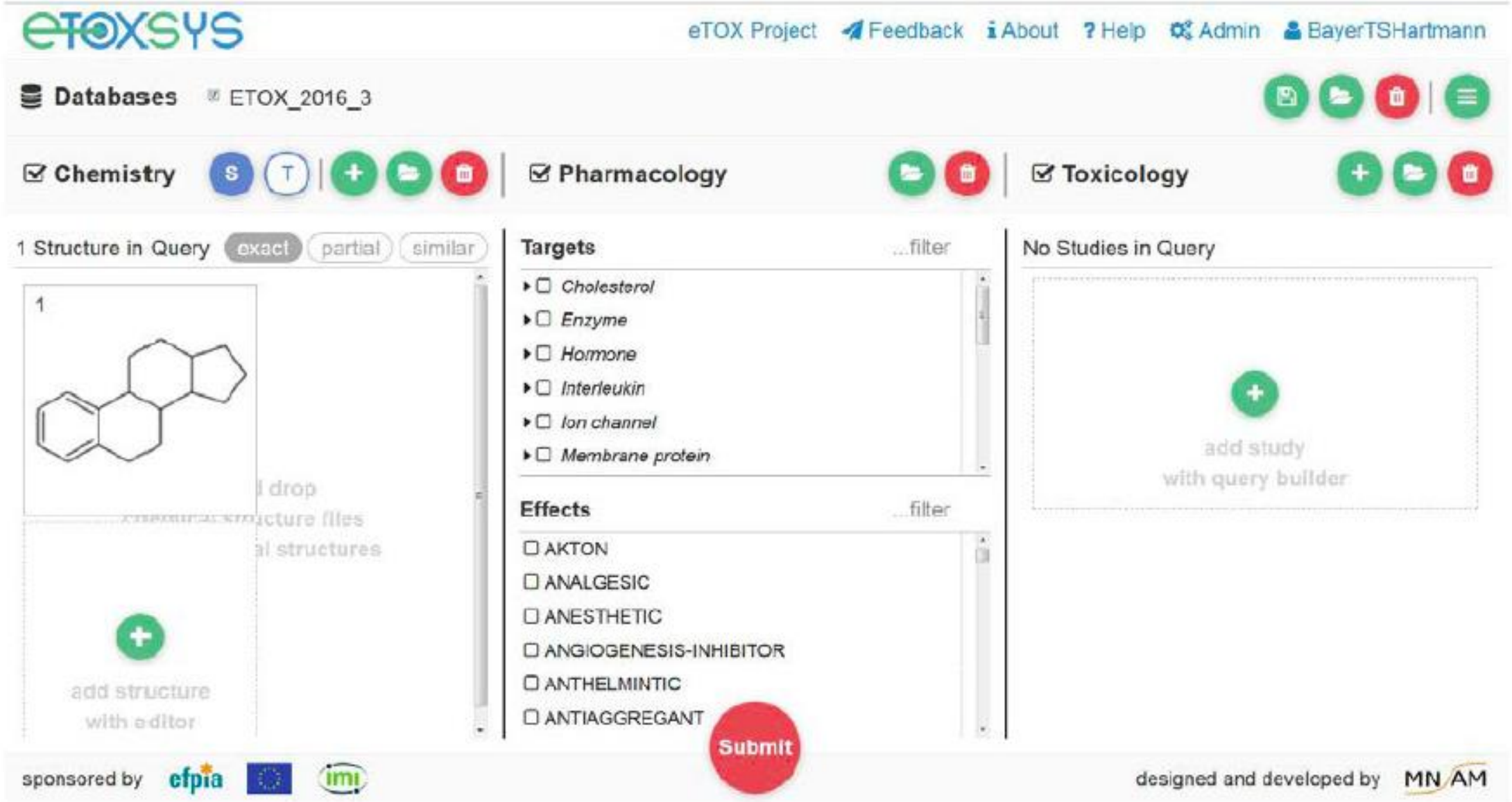
Research Article

Hepatotoxicity prediction by systems biology modeling of disturbed metabolic pathways using gene expression data

Pablo Carbonell[1,2], Oriol Lopez[1], Alexander Amberg[3], Manuel Pastor[1] and Ferran Sanz[1]*



eTOXsys software platform: Read-across



eTOXsys software platform: Predictive models

eTOXSYS

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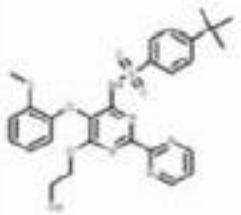
Prediction Jobs

Compounds/Mo...	Submitted...	Status
1 Compound	2017-1-3 9:6:21	SUCCESS
ABCB11 Inhibitio...		

Job Results: 1 Compound

Structure	ABCB11 Inhibition #1 (UNIVIE v1.0)...
	[no unit] Σ
	positive

Model Summary

ABCB11 Inhibition #1 (UNIVIE v1.0)

ABCB11 inhibitor classification model by UNIVIE (Version 1.0, 2013-04-13)

Endpoint:	ABCB11 Inhibition
Interpretation:	The model predicts if a query compound will be or not inhibitor of ABCB11. If "negative" is obtained, then the compound is predicted as non inhibitor of ABCB11. If "positive" is obtained, then the compound is predicted as inhibitor of ABCB11.
Unit:	
Keywords:	ATP-binding cassette transporter Bile salt export pump BSEP

eTOX efpia imi innovative medicines initiative

eTOX sustenaibility

- The eTOX IMI grant finished on Dec 31th, 2016.
- eTOX is entering into its sustainability phase.
- The eTOX partners are committed with the eTOXsys maintenance.
- eTOXsys consists of a unique database, a mature and professional software platform and a collection of useful models that makes attractive the commercial exploitation.
- Two SMEs (Lhasa and Molecular Networks) are managing such exploitation.
- The exploitation model is based on affordable fees for commercial users and symbolic ones for regulators and academic institutions.
- An eTOXsys Sampler including a subset of data and models will be public.

Main eTOX achievements

- ✓ **Open Innovation** through public-private multidisciplinary collaboration
- ✓ Unprecedented **information sharing** among the pharmaceutical companies
- ✓ **Integrative knowledge management** for better toxicological assessment, including pharmacokinetics and linkage with human drug safety information
- ✓ N**ew ontologies** required for data integration
- ✓ Tools supporting the community-based ontology development and curation (***OntoBrowser***)
- ✓ Transformation of the **raw toxicological data into variables relevant for predictive modelling**
- ✓ **Wide scope of predictive models**, incorporating complex modelling approaches (e.g. multi-scale models, systems biology)
- ✓ Platform for the development and maintenance of the models (***eTOXlab***)
- ✓ Detailed **verification and documentation and of the models**, including their reliability assessment (***ADAN***)
- ✓ Integrated and user-friendly **software platform** for read-across and use of the predictive models (***eTOXsys***)

Beyond eTOX: the IMI eTRANSAFE project

- Full Title: **Enhancing TRANslational SAFEty Assessment through Integrative Knowledge Management**
- Selected for funding within the **NexGETS IMI2 topic**
- Starting date: **September 2017**
- Duration: **5 years**
- Budget: **39.6 M€** (20 M€ EU funding + 19.6 M€ EFPIA contribution)
- Objectives beyond eTOX:
  - Incorporation of legacy data in **SEND format**
  - Interconnection of preclinical and clinical data for translational safety assessment
  - Advanced methods and tools for data mining, analysis and visualization
  - Internationally accepted guidelines for legacy data sharing

Many thanks for your attention!

http://www.etoxproject.eu/

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