OpenRiskNet

RISK ASSESSMENT E-INFRASTRUCTURE

WP1 Requirement Analysis, Outreach and Case Studies

Thomas Exner (DC)

General Assembly and 2nd annual meeting - 12-13 December 2018, Brussels (Belgium)

OpenRiskNet: Open e-Infrastructure to Support Data Sharing, Knowledge Integration and *in silico* Analysis and Modelling in Risk Assessment
Project Number 731075

WP1 Objectives

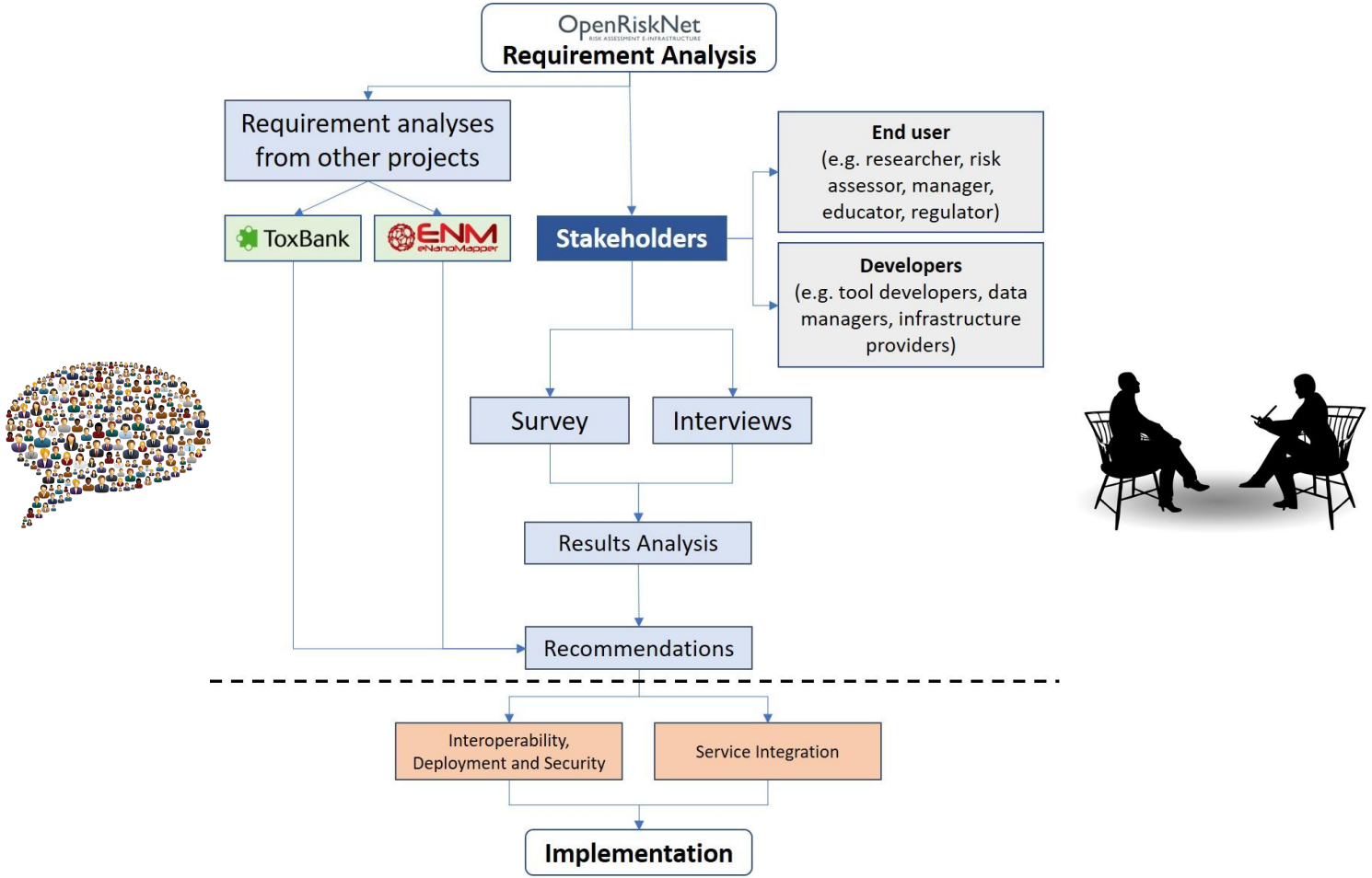
- **Requirement analysis:** Insights from stakeholders end users (*researchers, risk assessors and regulators in the fields of chemistry, pharma, cosmetics, nanomaterials*) as well as data providers, tool developers and workflow integrators regarding current challenges. (***Task 1.1**, 1 to 6 M*)

- **Outreach Program:** Directed towards current and past EU consortia as well as other related activities and individuals involved in the development of solutions for animal free risk assessment. (***Task 1.2**, 1 to 36 M*)

- **Case studies:** Testing the functionality of the e-infrastructure within the context of real-world applications. (***Task 1.3**, 1 to 36 M*)

T1.1: Requirement Analysis

Deliverable 1.1


OpenRiskNet
RISK ASSESSMENT E-INFRASTRUCTURE
Requirement Analysis
Requirement analyses from other projects
ToxBank
eNanoMapper
Stakeholders
End user
(e.g. researcher, risk assessor, manager, educator, regulator)
Developers
(e.g. tool developers, data managers, infrastructure providers)
Survey
Interviews
Results Analysis
Recommendations
Interoperability, Deployment and Security
Service Integration
Implementation

Task 1.1 Requirement analysis

Update of deliverable report D1.1:

- From survey: structured in Questions, Answers and Learnings
- Stronger relationship to case studies chosen
- Paper in preparation

Ongoing requirement analysis:

- Second version of requirements survey
- Ongoing interviews especially with industry stakeholders
- Introduction and demo webinars and presentations at conferences and workshops with strong focus on stakeholder/user feedback

T1.2: Community Outreach

Deliverable 1.2: 1.4

Task 1.2 Community Outreach

Webinars and conference/workshop presentations

- Introduction and demonstration webinars: 3 sessions a 2h with overall 70+ participants
- Poster and material at booth at the EuroTox conference
- Presentation and workshops at OpenTox Euro
- Presentation at the US nano working group
- Presentation at NanoKorea and Korea-EU nano workshop
- “Meet us” at different conferences including ESTIV, WikiPathway summit, UK QSAR,...
- Data annotation hackathon and ontology hackathon coorganized with NanoCommons

Complete list of dissemination activities: https://openrisknet.org/events/

Dissemination material

- Recordings of the webinars and copies of slides and posters in library
- Fliers presenting the infrastructure (distributed at the conferences)
- Roll-up presented at the infrastructure meeting in Vienna and OpenTox Euro

Complete list of dissemination materials: https://openrisknet.org/library/

Task 1.2 Community Outreach

Associated Partner Programme

To ensure the usability of the infrastructure, alignment with the community, as well as to pursue complete coverage of important data and tools for risk assessment

Officially launched at the OpenTox Euro 2017 conference (November 2017) >> Read the press release

- **Service providers** - integrate their databases and software tools into the OpenRiskNet infrastructure:
  - greater visibility of their tools by being listed in the OpenRiskNet discovery service;
  - infinite additional features by combining with other tools;
  - support for emerging techniques like API development and containerization/deployment.
- **Early adopters** - use the infrastructure for their predictive toxicology and risk assessment tasks:
  - easy access to a increasing number of tools using their preferred access route (web, workfl ow tools like knime, scripts) without the need of manually downloading of data and file conversion when moving from one tool to another;
  - harmonized access for comparison of different approaches.
- **Technology partners** - use their services and tools for the OpenRiskNet e-infrastructure development

https://openrisknet.org/associated-partner-programme/

Task 1.2 Community Outreach: Associated Partner Programme

Programme Guideline ✔

Standard Agreement ✔

1. **Service providers**
   a. Korea Institute of Toxicology
   b. Other Implementation Challenge winners
2. **Early adopters:**
   a. University of Oxford
   b. Diamond Light Source Ltd
   c. Andrew Nelson, University of Leeds
3. **Technology partners:**
   a. Red Hat
   b. Swedish National Infrastructure for Computing Science Cloud

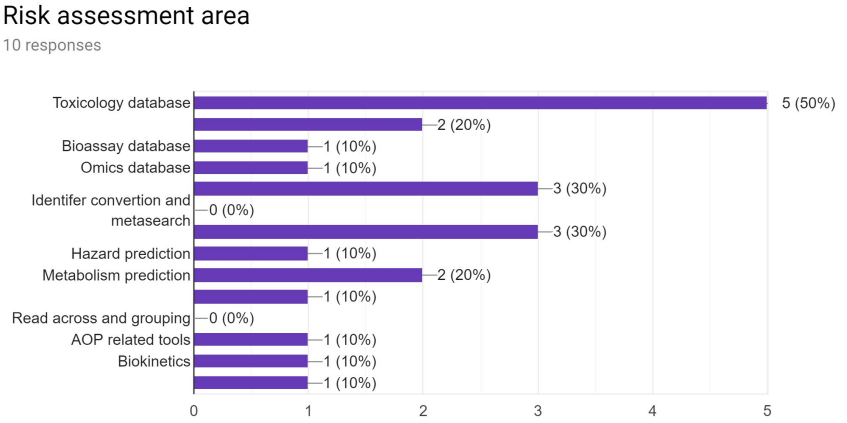
Task 1.2 Community Outreach: Implementation Challenge

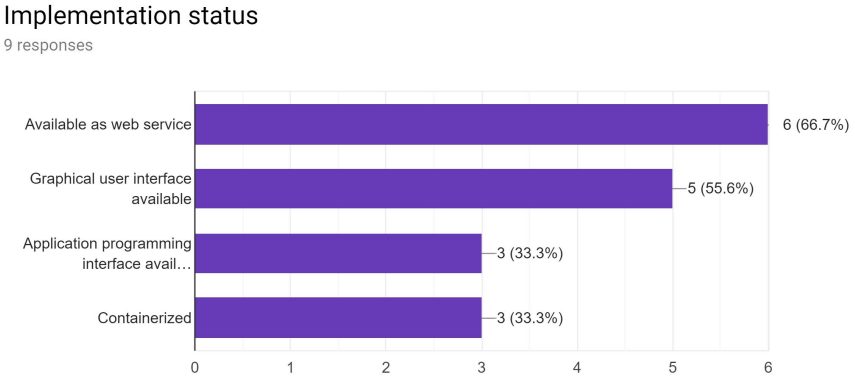
Deadlines for the implementation challenges are:
31 October 2018✔, 31 January 2019, 30 April 2019

First selection round: 10 applicants

6 winners selected by the Scientific Advisory Board

- Holly Mortensen, US EPA
- Hyun Kil Shin, Korea Institute of Toxicology
- Matthias Timberlake, ToxPlanet
- Johannes Kirchmair, Universität Hamburg
- Antreas Afantitis, NovaMechanics Ltd
- Igor Tetko, BIGCHEM GmbH





T1.3: Case Studies

Deliverable D1.3; D1.5
Milestone 3

SEURAT-1

Towards the Replacement of in vivo Repeated Dose Systemic Toxicity Testing

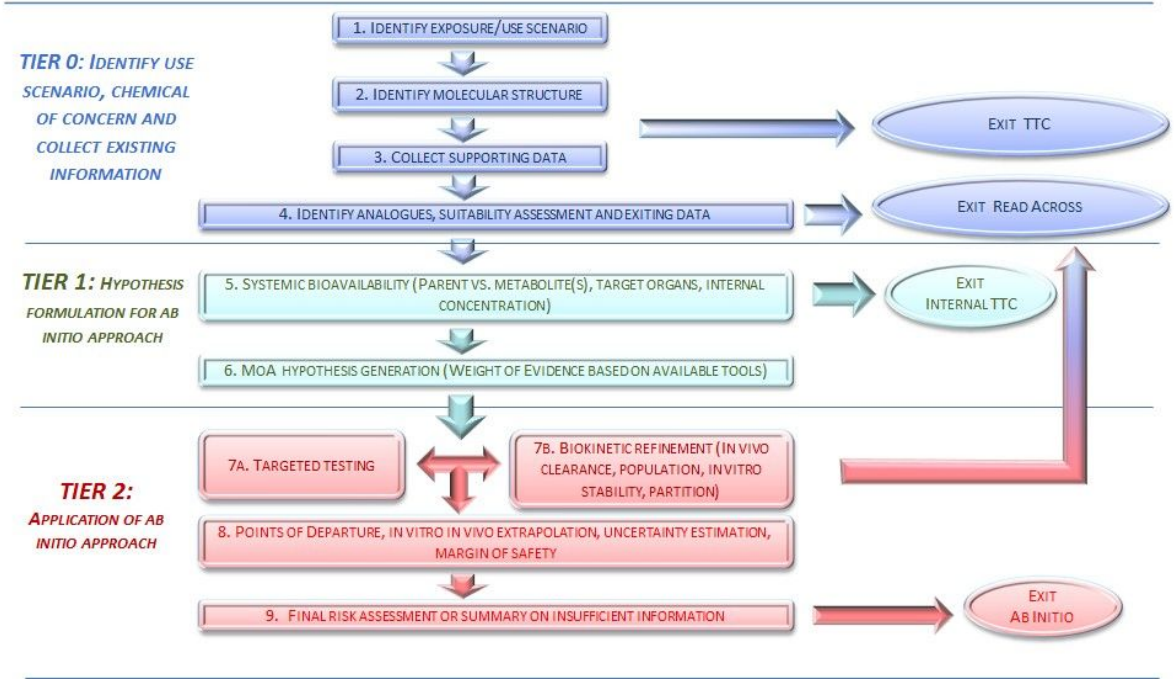
Sponsored Document from
Computational Toxicology ELSEVIER FREE Full-Text Article

Comput Toxicol. 2017 Nov; 4: 31–44.
Published online 2017 Nov. doi: 10.1016/j.comtox.2017.10.001

PMCID: PMC5695905
PMID: 29214231

Ab initio chemical safety assessment: A workflow based on exposure considerations and non-animal methods

Elisabet Berggren,[a,*] Andrew White,[b] Gladys Ouedraogo,[c] Alicia Paini,[a] Andrea-Nicole Richarz,[a] Frederic Y. Bois,[d] Thomas Exner,[e] Sofia Leite,[f] Leo A. van Grunsven,[f] Andrew Worth,[a] and Catherine Mahony[g]



CONCLUSION: This general "ab initio" workflow was developed as a means of structuring knowledge and data in a **logical sequence** for an integrated safety assessment applying non animal methods. **Workflow could be the basis for a full risk assessment and is aiming to provide a tool to guide the evaluation through the different steps to be considered and enable and gain confidence in decision making.**

The workflow is general enough to cover different types of chemicals, endpoints and exposure scenarios.

www.openrisknet.org

Case Studies: What is a case study ?

A particular instance of something used or analysed in order to illustrate a thesis or principle.

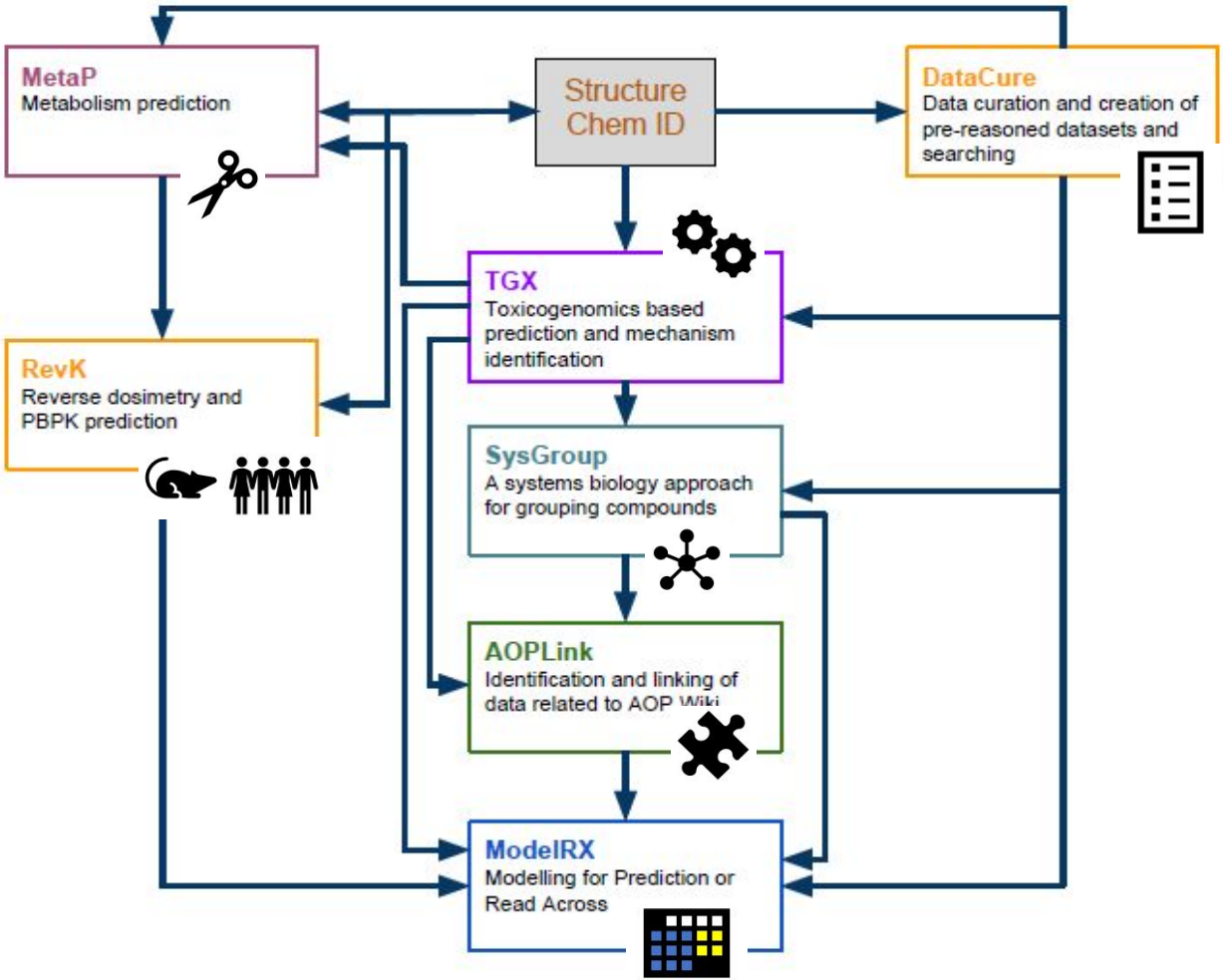
Is meant as:

- an in depth study of a particular situation
- method used to narrow down a very broad field of research into a researchable topic
- a guide to allow further elaboration and hypothesis creation on a subject
- an exercise to facilitate different disciplines to combine forces

Is not meant as

- a sweeping statistical survey
- a complete answer to a particular question completely

T1.3 Case Studies



Case Studies documentation and resources

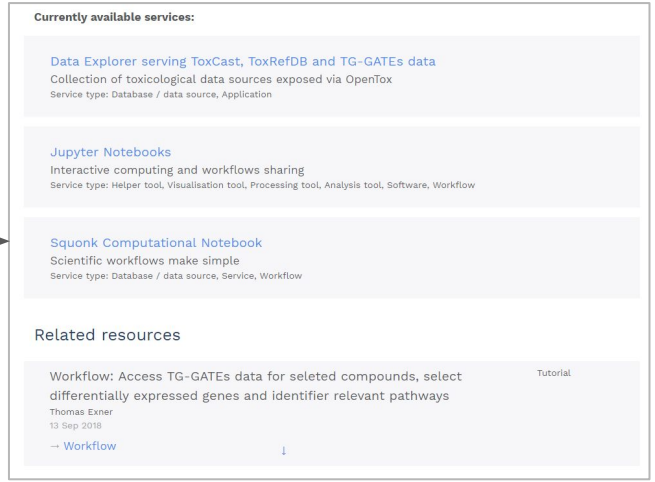
https://openrisknet.org/e-infrastructure/development/case-studies/

DataCure	Data curation and creation of pre-reasoned datasets and searching
ModelRX	Modelling for Prediction or Read Across
SysGroup	A systems biology approach for grouping compounds
MetaP	Metabolism Prediction
AOPLink	Identification and Linking of Data related to AOPWiki
TGX	Toxicogenomics-based prediction and mechanism identification
RevK	Reverse dosimetry and PBPK prediction

*Case studies **list***

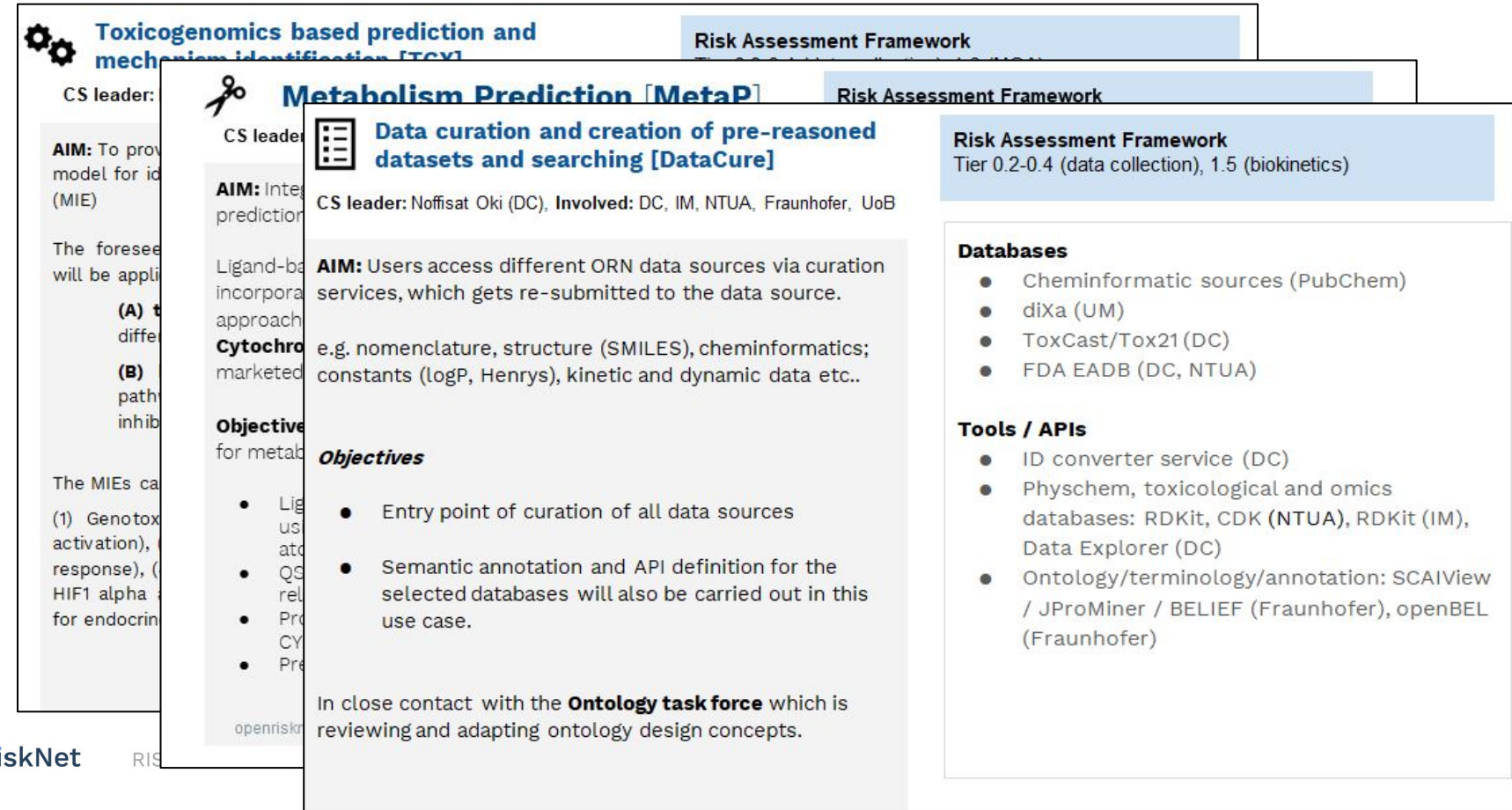
Summary
Objectives
Risk assessment framework
Use Cases Associated
Databases, tools and service integration

*Case studies **description***



***Services** and **resources** (e.g. workflows, training materials) available and linked from the e-infrastructure Catalogue or Library (example of DataCure case study)*

Task 1.3 Case study descriptions



Metabolism Prediction [MetaP]

CS leader: Daan Geerke (VU), **Involved:** UU, JGU, UHH

Risk Assessment Framework
Tier 0.1 (mol. structure), 1.5 (biokinetics), 1.6 (MoA)

AIM: Integration of tools for site-of-metabolism (SOM) prediction and metabolite prediction

Ligand-based metabolite predictors (e.g. MetPred) and incorporate protein-structure and -dynamics based approaches to predict the site of metabolism (SOM) by **Cytochrome P450 (CYPs)**, which metabolize ~75% of the currently marketed drugs.

Objectives: Integration, comparison and combination of tools for metabolism prediction

- Ligand-based Site-Of-Metabolism (SOM) prediction using reaction SMARTS, circular fingerprints and/or atomic reactivities
- QSBR (quantitative-structure biotransformation relationship) modeling of microbial biotransformation
- Protein-structure and -dynamics based prediction of CYP450 isoform specific binding and SOMs
- Predicting probabilities for specific reaction type events

openrisknet.org/e-infrastructure/development/case-studies/case-study-metap

Databases During method development, model calibration and validation we will use data from XMetDB and other open-access databases for drugs, xenobiotics and their respective metabolites.

XMetDB, SMARTcyp, ZINC, ChEMBL, EAWAG-BBD

Tools / APIs

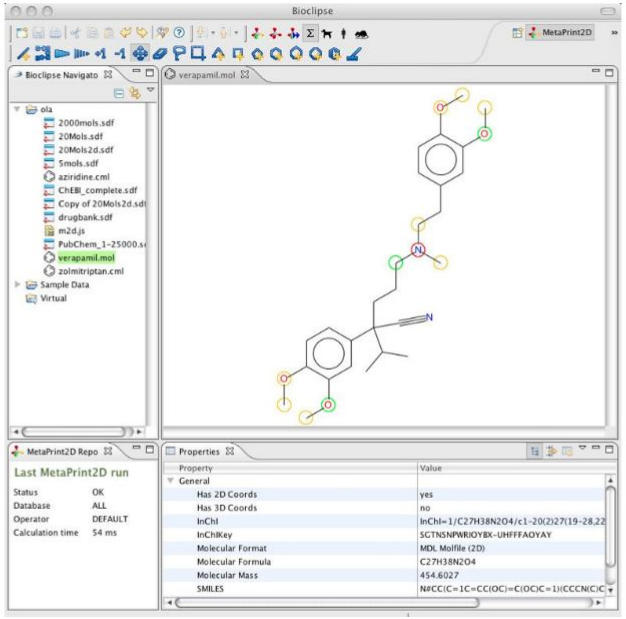
- MetPred (UU) (UU)
- Metaprint2D & MetVap (UU)
- UM-PPS (JGU)
- enviPath (JGU)
- SMARTCyp (external service, integration by VU)
- Plasticity tools (VU)
- FAME (UHH; implementation challenge)

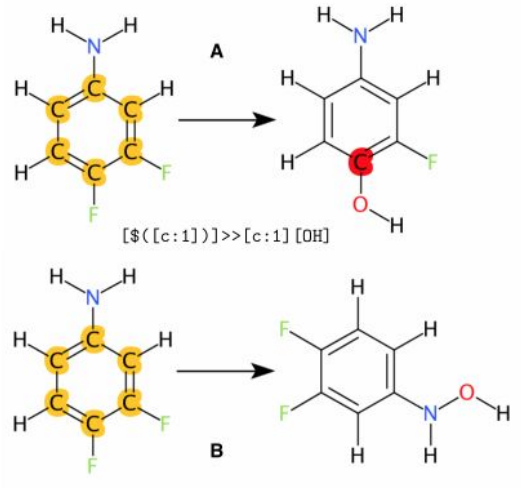
Service integration

To facilitate combining metabolite prediction approaches and using MetaP outcomes as input for other predictors, we will take advantage of ongoing development in workflow management systems (Nextflow, Squonk, MDStudio) and we will explore integration into/with and use of these platforms. Once integrated the added value of multiple predictors will be subject of a pilot study on metabolite prediction..

MetPred

Predicts phase I metabolites: MetPred ranks most probable sites-of-metabolism (SOMs) and reaction types based on similar atom environments and ReactionSMARTS in annotated dataset [webservice; API available]



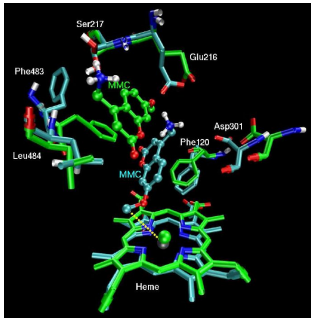


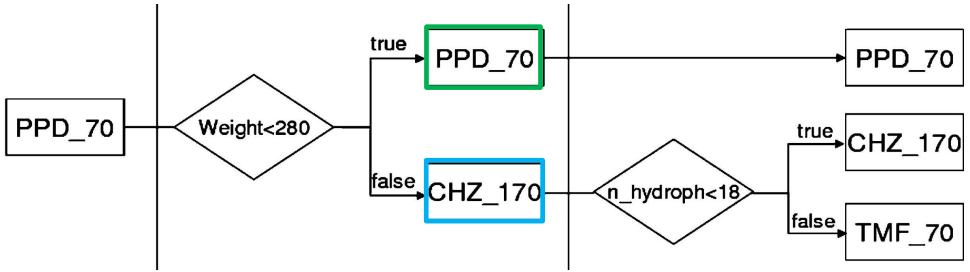
Carlsson et al. BMC Bioinformatics 2010
Arvidsson et al. Proc. Machine Learn. Res. 2017

Expanding the toolbox

Current focus:

- **FAME 2.0**: SOM prediction (also for phase I, phase II or enzyme/isoform specific metabolism) from machine learning using (<)15 quantum and circular-environment based atomic descriptors [implementation challenge]
- **enviPath**: prediction of microbial biotransformation pathways and products using rules represented by SMIRKS
- **SMARTCyp**: SOM prediction for P450 metabolism based on fragment-mapping to pre-computed high-level QM data and atomic accessibility, extended with simple ligand-based pharmacophore rules for specific isoforms
- **Protein-structure based predictors**: plasticity models for docking into (flexible) P450 isoforms





Adapted from Hritz et al. J Med Chem 2008

Complementary tools, and we will explore added value of combined use for e.g. **consensus prediction**

Acknowledgements

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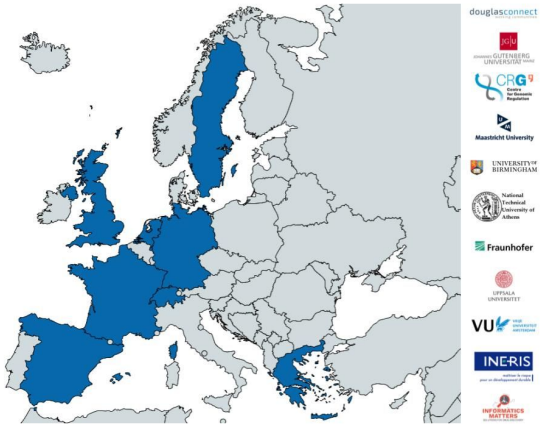
Project partners:



P1 Douglas Connect GmbH, Switzerland (DC)
P2 Johannes Gutenberg-Universität Mainz, Germany (JGU)
P3 Fundacio Centre De Regulacio Genomica, Spain (CRG)
P4 Universiteit Maastricht, Netherlands (UM)
P5 The University Of Birmingham, United Kingdom (UoB)
P6 National Technical University Of Athens, Greece (NTUA)
P7 Fraunhofer Gesellschaft Zur Foerderung Der Angewandten Forschung E.V., Germany (Fraunhofer)
P8 Uppsala Universitet, Sweden (UU)
P9 Medizinische Universität Innsbruck, Austria (MUI)
P10 Informatics Matters Limited, United Kingdom (IM)
P11 Institut National De L'environnement Et Des Risques INERIS, France (INERIS)
P12 Vrije Universiteit Amsterdam, Netherlands (VU)