OpenRiskNet

RISK ASSESSMENT E-INFRASTRUCTURE

Deliverable Report D1.3

Final definition of case studies

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

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SUMMARY

OpenRiskNet case studies are used to test and evaluate the solutions provided by the project to the predictive toxicology and risk assessment community especially regarding the usability of the developed Application Programming Interfaces (APIs) and the interoperability layer. These case studies will demonstrate the capabilities to satisfy the requirements of the different stakeholder groups including researchers, risk assessors and regulators and present real-world applications such as systems biology approaches for grouping compounds, read-across applications using chemical and biological similarity, and identifying areas of concern based on *in vitro* and *in silico* approaches for compounds lacking any previous knowledge from animal experiments (*ab initio* case).

The seven case studies (CS) depicted in **Figure 1** are defined in this report. The figure show the interrelationships between the studies combined, providing many components of risk assessment workflows. Besides these studies, additional ones will be defined in cooperation with partnering EU projects. The development of these studies can now progress following the official launch of the associated partner programme. To document the progress, case studies, associated use cases (*see Deliverable 2.2*), obtained results and lessons learned will be continuously made publicly available at: https://openrisknet.org/development/case-studies/.

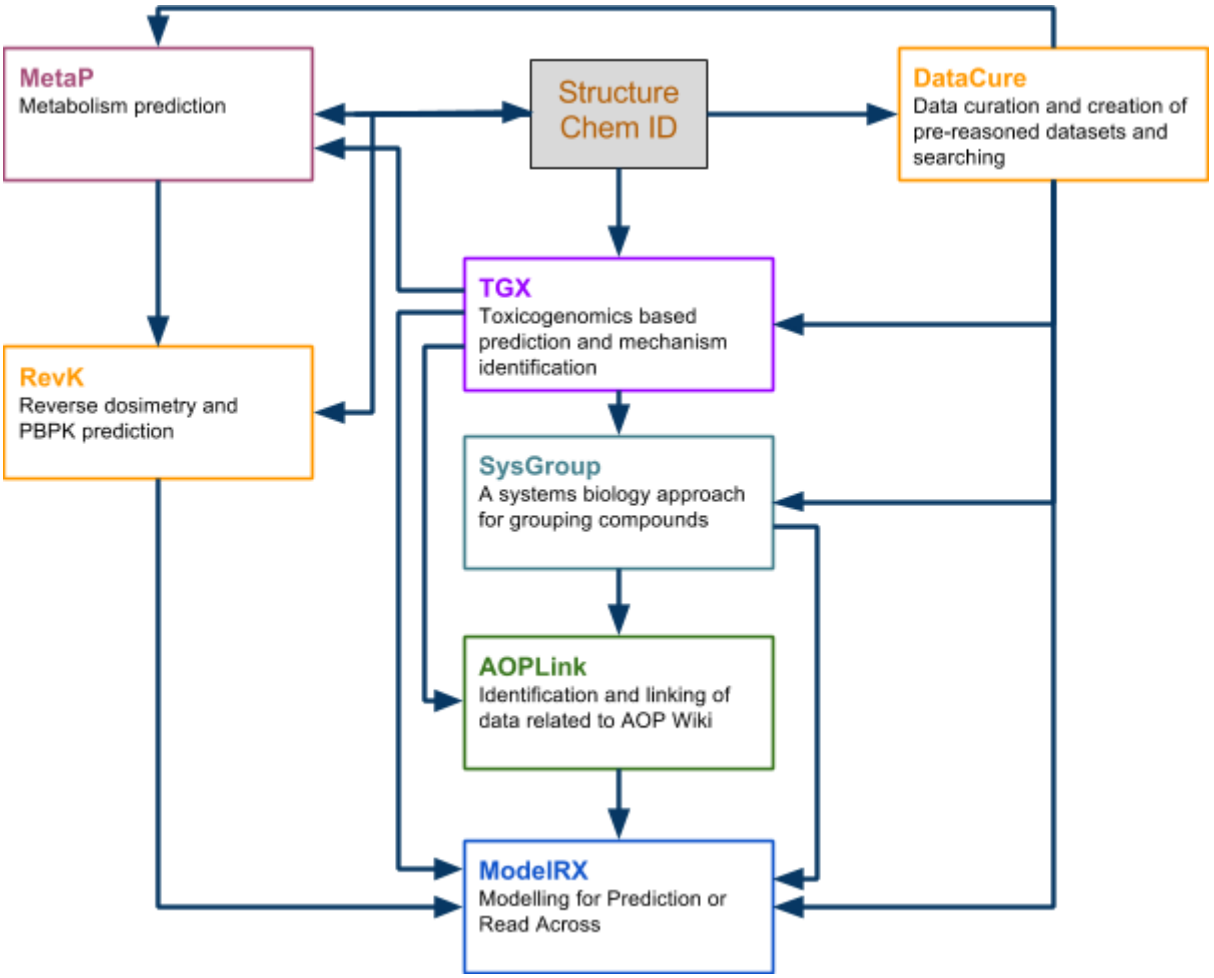

Figure 1. Case studies interconnection

INTRODUCTION

The aim of the OpenRiskNet project is to develop and deploy an integrated, secure, permanent, service driven and sustainable infrastructure for data managing, data sharing, processing, analysis, information mining and modelling as well as workflow development and sharing, visualisation and reporting to serve communities in the areas of toxicology, risk assessment and chemical, pharmaceutical, cosmetic and nanomaterial product development including safe-by-design aspects at an early stage. This e-infrastructure will support all aspects of risk assessment by allowing for the integration of all toxicology-related data sources, for the implementation and execution of processing and analysis pipelines and for the execution of modelling workflows for pharmacokinetics or pharmacodynamics. To demonstrate the features and functionality of the e-infrastructure (data, tools and services) using real-world application, the case studies defined in this document will create workflows for specific aspects of the risk assessment process and will apply these to examples of chemicals (including drugs, pesticides and cosmetic ingredients) and nanomaterials, for which data and reference results are available from case studies from previous and ongoing projects.

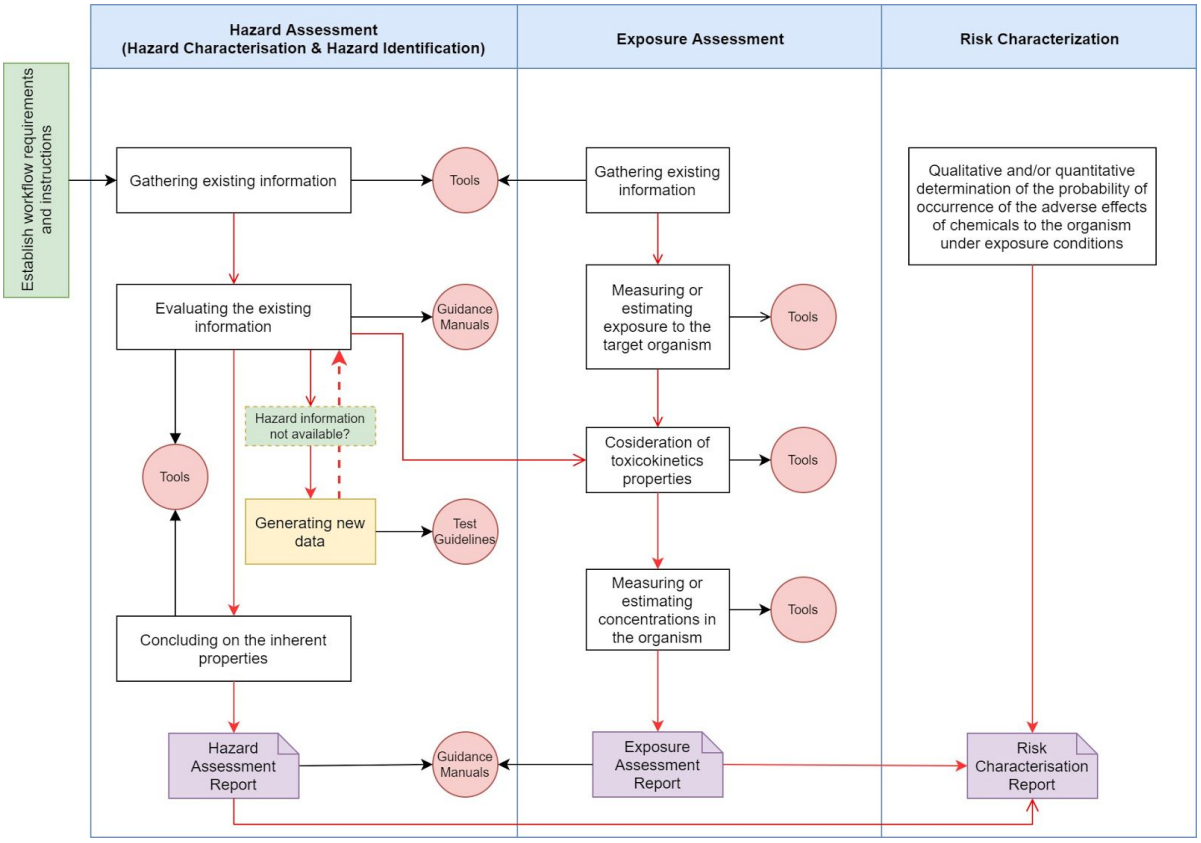

Figure 2. General risk assessment workflow (adapted from [1])

The process of risk assessment includes four steps (see **Figure 2**): hazard identification, hazard characterisation, exposure assessment and risk characterisation. The first two steps are regarded as the process of hazard assessment. The knowledge and data used in

this complex process has to be made available to risk assessors in an easy accessible, standardised and harmonised way in order to be able to base conclusions and recommendations on the safety of a chemical, drug, cosmetic ingredient and nanomaterial on all available evidence.

One measure used in different projects to demonstrate that the objectives of an project have been achieved and obtain general acceptance are case studies. Martyn Shuttleworth [2] defines a case study as “an in-depth study of a particular situation rather than a sweeping statistical survey. It is a method used to narrow down a very broad field of research into one easily researchable topic. Whilst it will not answer a question completely, it will give some indications and allow further elaboration and hypothesis creation on a subject. The case study research design is also useful for testing whether scientific theories and models actually work in the real world.” For OpenRiskNet this means probing specific aspects and functionalities of the e-infrastructure.

The goal in the first year of the project was to define and agree on these case studies which cover relevant scientific communities and identify a minimal set of databases and tools to further integrate into a functional e-infrastructure. The requirements analysis (*see Deliverable 1.1*) identified gaps in existing approaches and needs in the different communities. The extracted requirements, previous experience of partners and the developments in the first twelve months in the project were translated into 7 case studies, which will be executed and refined throughout the project. This will include the identification and integration of relevant data and knowledge sources, and identification and integration of algorithms and tools covering all important areas for risk assessment (e.g. toxicity predictions, toxicogenomics, biokinetics modelling, *in vitro - in vivo* extrapolation). Besides the fully-defined case studies described below, additional cases will be custom-made in cooperation with other EU-projects, which join the associated partner programme as early adopters (*see Deliverable 1.2*).

RISK ASSESSMENT FRAMEWORKS

To identify relevant areas in the risk assessment process, in which OpenRiskNet solutions could be highly beneficial, to see the coverage of all these areas by the case studies and to optimise their interconnection and interworking, different risk assessment approaches were investigated in order to be adopted as an overarching framework in OpenRiskNet, e.g. SEURAT-1 concept [3], ILSI-HESI RISK21 framework [4], a framework for the use of *in vitro*-derived biomarkers of toxicity in risk assessment [5], a data-driven framework [6] and finally the ab initio framework [7]. The latter workflow (see **Table 1**) was developed within the SEURAT-1 initiative [8] and was selected to guide our initial definition of the case studies. The aim of this is to implement an approach to assess chemical safety without relying on any animal testing, but instead constructing a hypothesis based on existing data, computational modelling, biokinetic considerations and then by targeted non-animal testing [7]. It is, in our opinion, the most complete framework developed so far, pushing the 3Rs concept (Replacement, Reduction and Refinement) to avoid animal testing to its limit, and still overlaps with the other frameworks to a large extent. However, for the further developments, other concepts will be added or followed in order to avoid any limitations created by a single framework, and this information will be incorporated into the related case study description.

Table 1. Workflow for the safety assessment of chemicals without animal testing (adapted from [7])

Tier	Steps in the framework
Tier 0 - Identification of use scenario / chemical of concern / collection of existing information	1. Identification of exposure / use scenario
	2. Identification of molecular structure
	3. Collection of support data
	4. Identification of analogues / suitability assessment and existing data
Tier 1 - Hypothesis formulation	5. Systemic bioavailability
	6. Mode of Action hypothesis generation
Tier 2 - Application of the approach	7A. Targeted testing
	7B. Biokinetic refinement
	8. Points of departure / IVIVE / uncertainty estimation / margin of safety
	9. Final risk assessment or summary on insufficient information

CASE STUDIES DEFINITION

The case studies defined so far are described below. Leader and core team members have been selected and have started their work. Over the duration of the case study work, these teams will be extended towards third parties joining the project through the associated partner programme (*see Deliverable 1.2*) providing additional services essential for the case studies or adding to the scientific expertise and defining new requirements.

Even if the full set of requirements were under development during the first year of the project, preparatory work on the cases was already started during this period. Initial testing and validation of basic concepts such as the OpenRiskNet APIs and the related semantic interoperability layer were carried out in parallel to the case study development to identify issues as soon as possible. To be able to do so, fully elaborated subparts of the case studies have been translated into use cases to evaluate important key components of the infrastructure.

A short introduction to the scientific goals pursued, the technical subareas of the infrastructure probed by the case studies and the relationship to the risk assessment framework of **Table 1** is given below with links to more information and updates. These studies will now guide the prioritisation of data sources and tools to be integrated and used as first examples to improve the interoperability level of the corresponding APIs with respect to harmonisation of the API endpoints, service description and semantic annotation.

Data curation and creation of pre-reasoned datasets and searching [**DataCure**]

Summary

Users will be able to access different OpenRiskNet data sources and specific entries. This can then be manually curated using an OpenRiskNet service and re-submitted to the data source. In an extended version, text mining facilities could be used for data annotation.

A first step will be to define the API and provide the semantic annotation for selected databases (i.e. diXa, FDA datasets, ToxCast and ChEMBL). During the preparation for these case studies it became clear that the existing ontologies are not covering all requirements of the semantic interoperability layer. Therefore, ontology development and design of the annotation process as an online or an offline/preprocessing step form a central part of this case study.

CS leader	Team
Noffisat Oki (DC)	DC, IM, NTUA, Fraunhofer, UoB

Objectives

- This case study will serve as the entry point of curation of all data sources to be used by the remaining use cases;
- Semantic annotation and API definition for the selected databases will also be carried out in this use case.

Risk assessment framework

DataCure covers the identification of use scenario / chemical of concern / collection of existing information (Tier 0 in the selected framework) and its steps related to:

- Identification of molecular structure;
- Collection of support data;
- Identification of analogues / suitability assessment and existing data.

Use Cases Associated

This case study is associated with UC1 - Merge existing data by a common structure identifier [9], where a user searches for existing assay information, selects the desired information, and merges the results based on a unique structure identifier. Specifically, the steps to achieve different objectives of the DataCure, include:

- The user identifies and visualises the molecular structure:
    1. Generation of molecular identifiers for database search
    2. Searching all databases
    3. Data curation
    4. Tabular representation
    5. Visualisation
- The user collects support data:
    1. Provide data access scheme using the interoperability layer
    2. Access selected databases or flat files in a directory
    3. Query to ontology metadata service and select ontologies, which should be used for annotation
    4. Annotate and index all data sets using text mining extraction infrastructure

5. Passing to ontology reasoning infrastructure
6. Generate database of pre-reasoned dataset (semantic integration)
7. Allow for manual curation

- The user identifies chemical analogues:
  1. Inventory of molecules (commercially available or listed in databases)
  2. Generate list of chemically similar compounds
  3. Collect data of similar compounds

Databases and tools

The following set of data and tools are proposed to be used and exploited within the DataCure:

- Physchem, toxicological and omics databases: RDKit, CDK, Chemical Identifier Resolver (NIH), PubChem, registries (e.g. ECHA, INCI), Data Explorer (DC);
- Ontology/terminology/annotation: SCAIView / JProMiner / BELIEF (Fraunhofer), openBEL.

Service integration

A set of physical-chemical properties prediction and ontology services will be integrated.

Modelling for Prediction or Read Across [**ModelRX**]

Summary

A training data set will be obtained from an OpenRiskNet data source. The model has then to be trained with OpenRiskNet modelling tools and the resulting model has to be packaged into a container, documented and ontologically annotated. The model will be validated using OECD guidelines. Finally, a prediction can be run.

CS leader	Team
Harry Sarimveis (NTUA)	NTUA, JGU, UU

Objectives

The objectives of this CS are: support similarity identification in the DataCure CS (by providing tools for calculating theoretical descriptors of substances), fill gaps in incomplete datasets and use *in-silico* predictive modelling approaches (read-across, QSAR) to support final risk assessment.

Risk assessment framework

The ModelRX CS contributes in two tiers:

- On the one hand, provides computational methods to support suitability assessment of existing data and identification of analogues (Tier 0).
- Secondly, it provides predictive modelling functionalities, which are essential in the field of final risk assessment (Tier 2).

Associated Use Cases

The ModelRX CS is associated with UC2 - Building and using a prediction model [10] including the pseudocode[1].

1. The user selects an algorithm and a dataset within the system to induce a model. The selection of the algorithm is based on the intended uses within a supervised setting (classification or regression problem, size of dataset, ability to select descriptors etc.)
2. The algorithm possesses a number of default parameters, which can be adjusted to the users' specifications.
3. The user starts the induction process.
4. Upon termination of the algorithm the user receives the result in the form of a model.
5. The user can supply an already existing second dataset and apply the model to it.
6. The results are returned as a novel dataset URI.

Databases and tools

JaqPot Quattro (NTUA), CPSign (UU), JGU WEKA Rest service (JGU), (Nano-)Lazar (JGU/IST).

Service integration

[1] https://github.com/OpenRiskNet/home/wiki/UseCase-2-Pseudocode

Modelling APIs need a high level of integration into the OpenRiskNet ecosystem. Integration with the DataCure CS is vital. On the semantic interoperability layer, training datasets should be compatible with an algorithm and prediction datasets should be compatible with a prediction model. Additionally, the generated models and datasets need to be accompanied with semantic metadata on their life cycle, thus enforcing semantic enrichment of the dynamically-created entities.

A systems biology approach for grouping compounds [**SysGroup**]

Summary

This case study will use the approach of the diXa / DECO2 (Cefic-LRI AIMT4) projects to reproduce and extend the results obtained on the identification of hepatotoxicant groups based on similarity in mechanisms of action (omics-based) and chemical structure using services from OpenRiskNet.

CS leader	Team
Danyel Jennen (UM)	UM, Fraunhofer, CRG

Objectives

The objective of this CS is to implement an integrated analysis using chemoinformatics and omics data for improved grouping of compounds with similar toxicity and/or mode of action.

Risk assessment framework

SysGroup covers the identification of use scenario / chemical of concern / collection of existing information (Tier 0 in the selected framework) and its steps related to:

- Identification of molecular structure
- Collection of support data
- Identification of analogues / suitability assessment and existing data

Associated Use Cases

This case study is associated with UC1 - Merge existing data by a common chemical identifier [9] and includes the following steps:

1. Chemical similarity calculated by 2D or 3D Tanimoto coefficient
2. Protein target prediction
3. Interface to diXa for obtaining gene expression data
4. Integration of the multiple data sources and grouping by iClusterPlus

Databases and tools

PubChem for Tanimoto scores, ChEMBL or PIDGIN for target predictions, (pre)processing tools for gene expression data (e.g. microarray data) and iClusterPlus for the integration of the multiple types of date.

Service integration

Integration with other case studies is needed. SysGroup acquires information from the DataCure CS and can feed into AOPLink and ModelRX.

Metabolism Prediction [**MetaP**]

Summary

Metabolites may well play an important role in adverse effects of parent drug (or other xenobiotic) compounds. In this case study we use and integrate ligand-based metabolite predictors (e.g. MetPred, MetaPrint2D) and we will implement protein-structure and -dynamics based approaches to predict the site of metabolism (SOM) by Cytochrome P450 enzymes, which metabolize ~75% of the currently marketed drugs and their active-site shape and plasticity often play an important role in determining the substrate's SOM. 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.

CS leader	Team
Daan Geerke (VU)	VU, UU

Objectives

For metabolite prediction we will develop, integrate and combine tools for:

- Protein-structure and -dynamics based prediction of CYP450 metabolite formation
- Inclusion of reactivity descriptors in the structure-based predictions
- Affinity and selectivity models for CYP450 binding
- Site-Of-Metabolism prediction using circular fingerprints
- Predicting probabilities for specific reaction type events

Risk assessment framework

Prediction outcomes can serve as input for other molecular structure-based AO predictors, which relates to Tier 0 (Step 1: identification of molecular structure) and Tier 1 (Step 6: mechanism of action).

Use Cases Associated

MetaP is associated with UC2 - Building and using a prediction model [10]. For improved metabolite prediction (and thereby improved input for other predictors) we will explore the potential of combining different approaches.

Databases and tools

XMetDB, SMARTcyp, ZINC, ChEMBL, MetPred, MetaPrint2D, ParaDocks, PLANTS, GROMACS.

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.

Identification and Linking of Data related to AOPWiki [**AOPLink**]

Summary

The Adverse Outcome Pathway (AOP) concept has been introduced to support risk assessment [11]. An AOP comprises a number of events and the adverse outcome: a molecular initiation event (MIE) is followed by one or more key events (KEs), leading to the adverse outcome (AO). The AOPWiki [12] is a collaborative to exchange AOPs.

The use of AOPs for regulatory purposes requires detailed validation and linking to existing knowledge [13,14]. Part of the development of AOPs is the search for data that supports the occurrence and biological plausibility of KEs and their relations (KERs). This data can be found in literature and increasingly in databases.

This case study focuses on establishing links between AOPs and data that supports a particular AOP. This will allow finding AOPs related to experimental data, and finding data related to a particular AOP.

CS leader	Team
Egon Willighagen (UM)	UM, DC, UoB, CRG

Objectives

For this case study we aim to develop:

- FAIR version of AOPWiki and WikiPathways;
- Identifier mappings for MIEs, KEs, and biological and chemical entities (genes, proteins, metabolites);
- Establish links between MIEs and KEs to biological assays;
- Establish links between assays and biological and chemical entities;
- Establish interoperable databases (see below).

Risk assessment framework

AOPLink will allow finding relevant experimental data for given compounds and nanomaterials and KEs (Tier 0, step 3), identify biological processes affected by exposure to those chemicals supporting hypothesis generation (Tier 1, step 6), and using these sources of information to determine if an AOP can be applied to that chemical and if not what information is missing (Tier 3, step 9).

With respect to the other case studies, AOPLink can take as input from SysGroup on similar chemicals (same group) in case no direct search results are found. Furthermore, TGX may provide predicted data to complement experimental data, to support searching. Because AOPLink may result in hypothesis and list KERs, these results can be passed to ModelRX for further prediction and read across.

Use Cases Associated

UC3 - Search and Retrieve Assay Data based on Ontological Terms [15].

Databases and tools

- AOPWiki, AOP knowledgebase (AOPKB);

- WikiPathways, Reactome: biological pathway database;
- BridgeDb: identifier mapping;
- diXa, BioStudies, ArrayExpress, etc: experimental data;
- Effectopedia, PathVisio: pathway analysis;
- PubMed, ContentMine: literature for key events and their molecular processes.

Service integration

Services provided by SysGroup:

- Grouping service that takes a compound or nanomaterial.

Services provided by TGX:

- API to access predicted data.

Other services:

- Search capability for the aforementioned databases;
- Identifier mapping service;
- PathVisioRPC;
- Text mining services to find relevant literature.

Toxicogenomics-based prediction and mechanism identification [**TGX**]

Summary

In this case study a transcriptomics-based hazard prediction model for identification of specific molecular initiating events (MIE) will be applied based on (A) top down and (B) bottom up approaches.

The MIEs can include, but are not limited to: (1) Genotoxicity (p53 activation). (2) Oxidative stress (Nrf2 activation). (3) Endoplasmic Reticulum Stress (unfolded protein response). (4) Dioxin-like activity (AhR receptor activation). (5) HIF1 alpha activation. (6) Nuclear receptor activation (eg for endocrine disruption).

CS leader	Team
Danyel Jennen (UM)	VU, CRG

Objectives

- Creation of prediction models based on differentially regulated genes (top down approach)
- Using knowledge of stress response pathways to integrate data sets for their activation or inhibition (bottom up approach)

Risk assessment framework

This CS is associated with all 3 tiers of the selected framework and in particular the following steps:

- Collection of support data
- Identification of analogues / suitability assessment and existing data
- Mode of Action hypothesis generation

Associated Use Cases

This CS is associated with UC1 [9] and UC2 [10].

These two use cases are relevant for the top down approaches:

- Reproducing the prediction models published by Herwig *et al* (2016) using data from the EU-project carcinoGENOMICs
- Advanced predictions using as much data as possible from the diXa data warehouse and other repositories giving free access to the data.

Databases and tools

Databases: diXa (carcinoGENOMICs, Predict-IV) TG-GATEs EU-ToxRisk (nascent) HeCaToS (nascent) ArrayExpress/GEO BioStudies.

Tools:

- top down: Data normalisation tools, prediction tools such as Caret
- bottom up: ToxPi

Service integration

Service integration will be needed for the *omics databases; knowledge bases and data mining; processing and analysis.

Reverse dosimetry and PBPK prediction [**RevK**]

Summary

In this case study the Open Systems Pharmacology physiologically based pharmacokinetic (PBPK) model will be made accessible, and used for risk assessment-relevant scenarios.

CS leader	Team
Frederic Bois (INERIS)	INERIS, NTUA, DC

Objectives

- Reverse dosimetry (finding the exposure dose of a chemical leading to a prescribed blood plasma concentration);
- Forward predictions of plasma and tissue concentrations following a prescribed exposure dose or concentration. In this case, Monte Carlo simulations of inter-individual variability will also be performed.

Risk assessment framework

This case study is particularly associated with Tier 2, step 7B (biokinetic refinements). PBPK models tend to be information hungry and are typically reserved to higher tier problems. However, there is a current push toward their use in lower prioritization tiers. This typically requires integration of databases and in silico models to inform PBPK parameter values.

Use Cases Associated

To be defined

Databases and tools

JaqPot Quattro (NTUA), PK-SIM (Open Systems Pharmacology, see web-site at https://github.com/Open-Systems-Pharmacology)

Service integration

A predictive pharmacokinetic model will be integrated.

CONCLUSION

Case studies are used in the OpenRiskNet project to evaluate the solutions provided by the project in real-world applications especially regarding the usability of the developed APIs and the interoperability layer and to demonstrate the capabilities to satisfy the requirements of the different stakeholder groups including researchers, risk assessors and regulators. Seven such case studies have been described in this report and the work on these has been started. They will now guide the prioritisation of data sources and tools to be integrated and used as first examples to improve the level of the corresponding APIs with respect to harmonisation of the API endpoints, service description and semantic annotation.

Additionally, the work on the case studies will now be opened up to third partners joining the OpenRiskNet project as associated partners in two ways:

1. Adding custom-made case studies for and in cooperation with other EU projects;
2. Strengthening the case study teams by inviting associated partners, who will provide services not available by the OpenRiskNet consortium, give scientific advice, evaluate the provided solutions and formulate new requirements.

GLOSSARY

The list of terms or abbreviations with the definitions, used in the context of OpenRiskNet project and the e-infrastructure development is available:

https://github.com/OpenRiskNet/home/wiki/Glossary

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ANNEXES

Annex 1. Case studies description template

TITLE
Title and acronym

SUMMARY
Summary description and the case study workflow / scheme (where relevant)

DESCRIPTION

Implementation team
Case study leader and the team

Objective(s)

Risk assessment framework
Link to an existing RA framework

DEVELOPMENT

Use Cases Associated

Databases and tools

Technical implementation

OUTCOMES

REFERENCES

Author(s), Title, Journal, Year, Vol, Issue Page, DOI

ANNEXES

Additional technical materials