

# AI-assisted Next Generation Risk Assessment and Safe and Sustainable Design Workflows enabled by FAIR Data and Knowledge

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*including collaboration with:*

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- Tom Luechtefeld and **InSilica** team
- Erik Schultes and **GOFAIR** team
- Collaborating partners on **RISK-HUNT3R**, **ONTOX**, **PrecisionTox** and **SSbD4Chem**
- Industry Case Study Partners

**ECETOC Workshop**

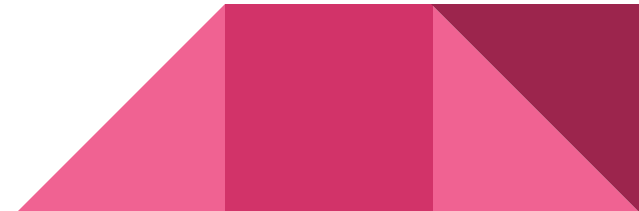
16-17 October 2024

Sophia Antipolis, France

*Integrating AI into Chemical Safety Assessment*

# Overview

1	Issues and Methodology
2	Cases and Applications
3	Sources of Knowledge
4	Practices and Standards
5	Legal and Ethics
6	Use Case Example
7	Outlook



# 01 Issues and Methodology

# Goals

- Develop robust evidence-based risk assessment practices and solutions
- Prepare reliable data and knowledge supporting risk assessment
- Use and refine AI approaches to enable knowledge management
- Optimise knowledge-driven AI approaches to assist risk assessment
- Support Human-AI collaboration including curation and analysis
- Test methods and practices against use cases and case studies
- Include open standards and best practices as a goal accelerator
- Align with developing AI practices and standards (trust, explainability, transparency, ethics, legal requirements)

# Issues

- Significant variation in quality of data, *a lot of historical data is not very FAIR, may not have followed best practice protocols e.g., in kinetics modelling for dose range setting or has incomplete protocol and metadata description*
- Significant variation in quality of literature, *following a systematic review one may reject 95% or more of the reviewed articles as not matching evidence quality criteria*
- Significant amount of traditional high quality toxicology data is firewalled; *need for data sharing mechanisms which currently are limited*
- Preparation of FAIR data and knowledge is time and resource expensive; *quality has a cost but also needs convincing business cases*
- New approach methods supporting risk assessment often still have limited datasets and regulatory acceptance
- We have often agreed on the benefits of open standards and ontologies, *but coordinated support and engagement has often been disjointed with insufficient sustainable adoption*
- Risk assessment lacks a structured practice, *with significant variation in results obtained*
- New forms of AI often have limited expertise and thematic training, *provide results of uncertain quality*
- Increasing amount of “AI junk” on the internet and accelerated by social media lacking facts or truth, further exacerbating poor quality of digested *knowledge, curation of knowledge is becoming a a critical function*

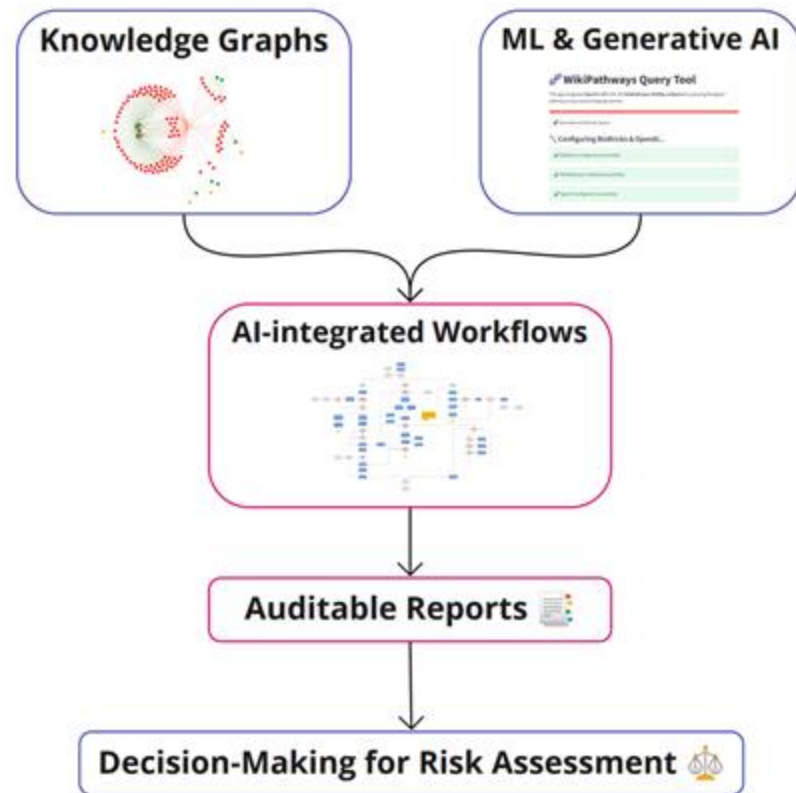
# Approach

- Define Use Cases supporting risk assessment (e.g., search for all current information, define compound testing set, evaluate a concern related to metabolism, execute a task in a step of an SSbD workflow)
- Define (Draft) Business Cases (and test and refine them!)
- Agree problem formulations and case studies to be tested against
- Test use cases with and without use of (non-FAIR and FAIR-based) AI and compare results for quality, completeness, accuracy, transparency, costs, *including results from different sources of knowledge, and filtering/curation mechanisms*
- *Follow Principles of the OpenTox Framework 2.0 (original framework updated for developments over the last decade and especially with attention paid to recent AGI developments such as LLMs; article in preparation for OpenTox 2024 (25-29 November)\* and In Vitro Toxicology)*

\* <https://www.opentox.net/events/virtual-conference-2024>

# Risk Assessment Test Cases

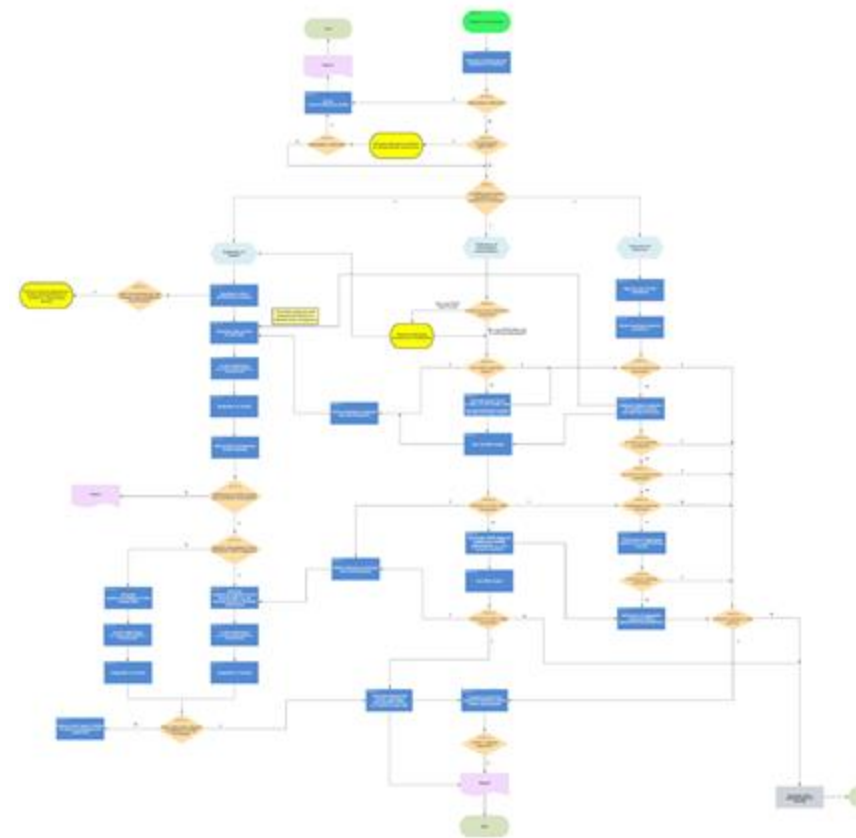
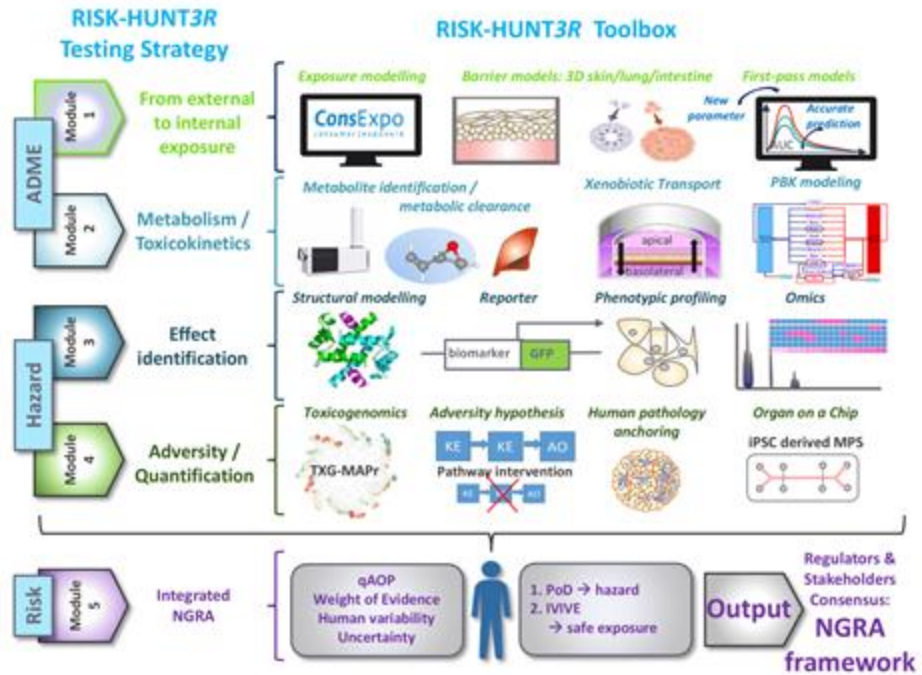
1. Efficient retrieval of well-referenced knowledge via a knowledge graph.
2. Enhanced toxicology learning with ML and Generative AI.
3. AI-integrated workflows for risk assessment and decision-making.
4. Auditable reports with supporting data for risk assessments.



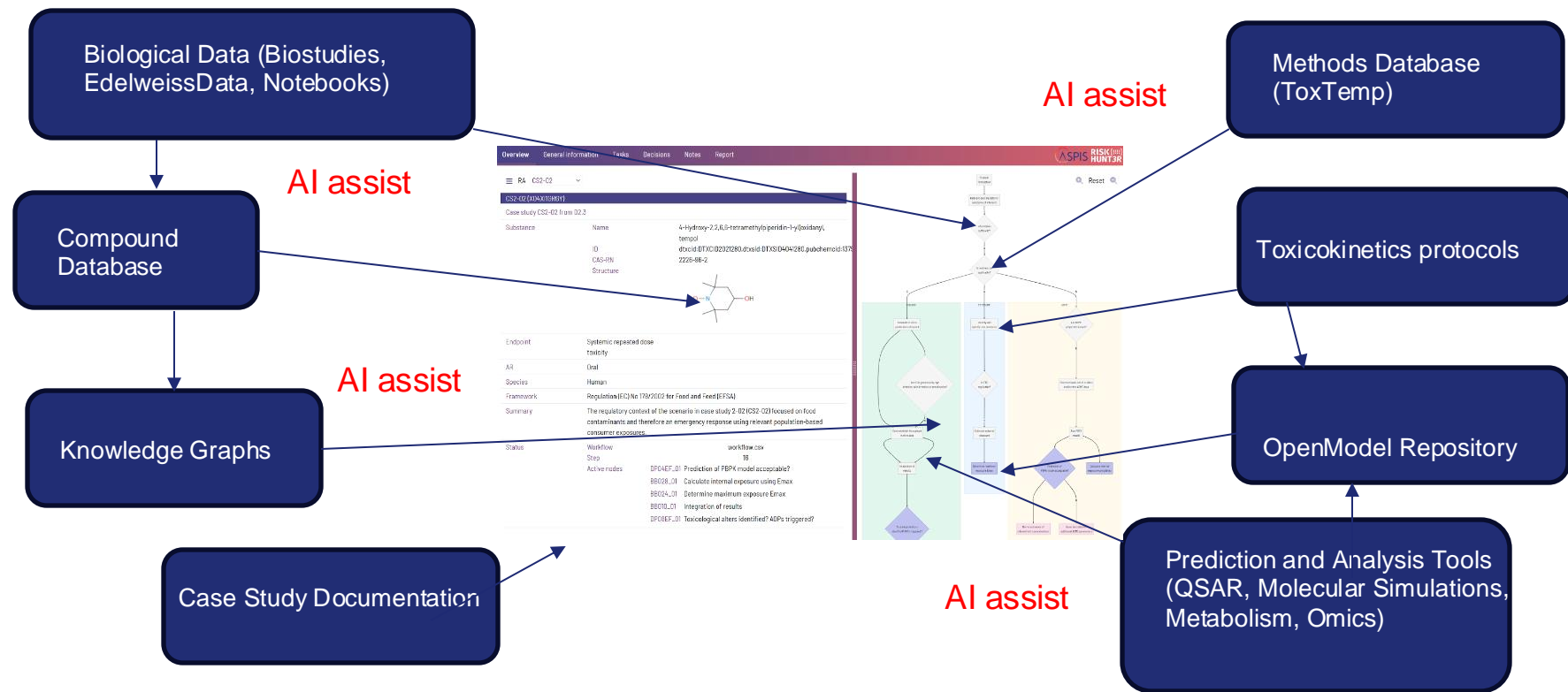
# 02 Cases and Applications




































# NGRA and ASPA Workflows



# Knowledge Infrastructure Support of ASPA Workflow



# Safe and Sustainable by Design Infrastructure and Case Studies (SSbD4Chem)

SSbD4Chem framework and workflow						
EdelweissConnect	ENTELOS INSTITUTE	Characterization	Computer aided (re)design approach	Human health and environmental safety assessment	Exposure assessment / risk management	Sustainability assessment across the life cycle assessment
 <b>AUTOMOTIVE</b>  	<b>Time-of-flight mass spectrometry</b> 	<b>Computational Fluids Dynamics</b> 	<b>hiPSC-based <i>in vitro</i> lung model</b> 	<b>Reduced TVOC emissions</b>   	<b>LCA, s-LCA, and LCC</b>   	
 <b>TEXTILE</b>  	<b>High resolution chemical imaging</b> 	<b>Molecular simulations</b> 	<b>Zebrafish embryo model</b> 	<b>Characterisation of microfibers and microfibrils release</b>  	<b>LCA, s-LCA, and LCC</b>   	
 <b>COSMETICS</b>  	<b>Field-Flow Fractionation hyphenated to light scattering</b> 	<b>Machine learning toxicity models</b> 	<b>Human skin <i>ex vivo</i> and <i>in vitro</i> models</b> 	<b>Fate and the behaviour in the environment</b> 	<b>LCA, s-LCA, and LCC</b>   	

D&C&E BNN

Funded by the European Union

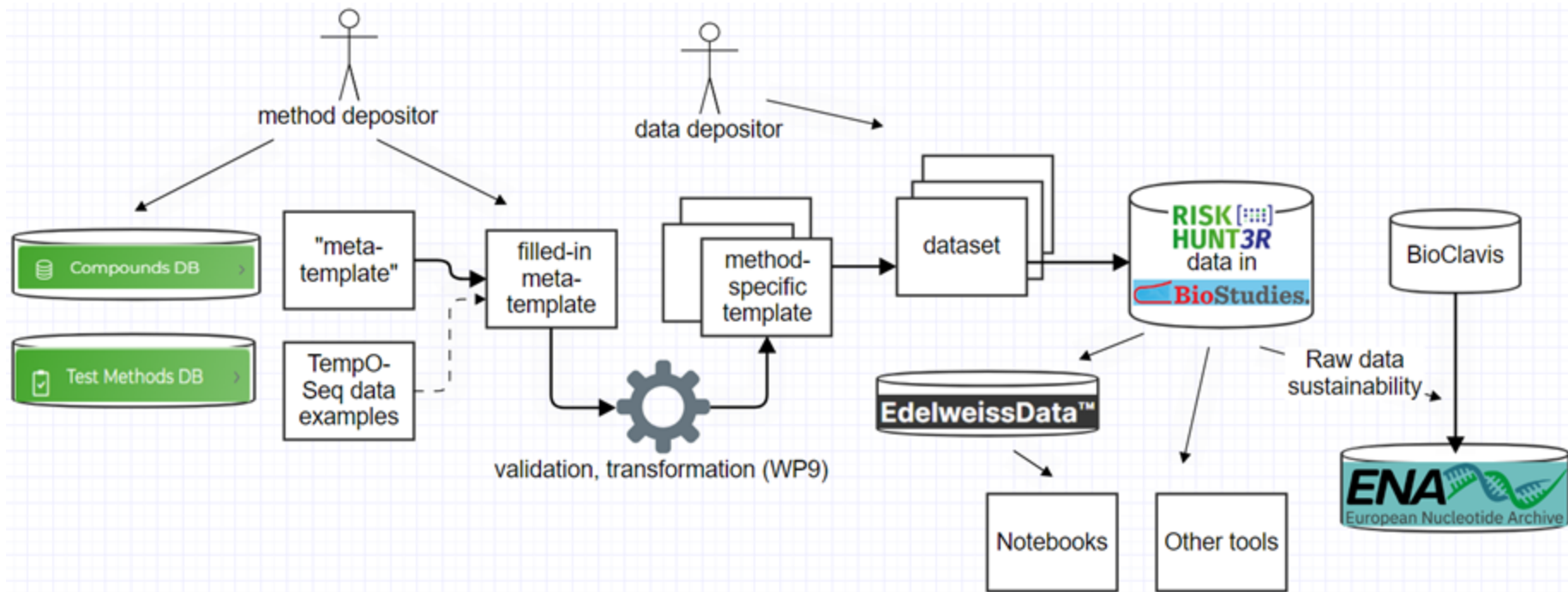
UK Research and Innovation

Project funded by:  

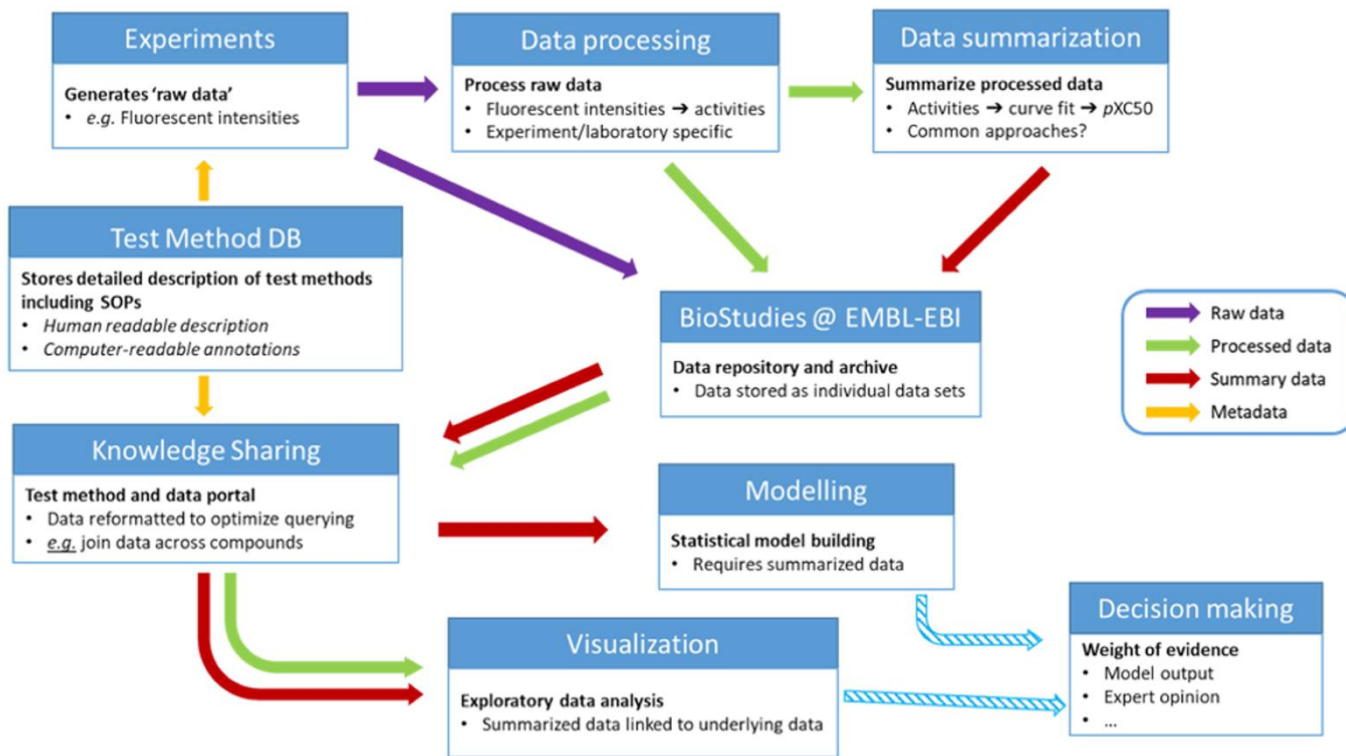



# 03 Sources of Knowledge

# FAIR Data Processing Workflow



# FAIR Knowledge Infrastructure (EU - ToxRisk)



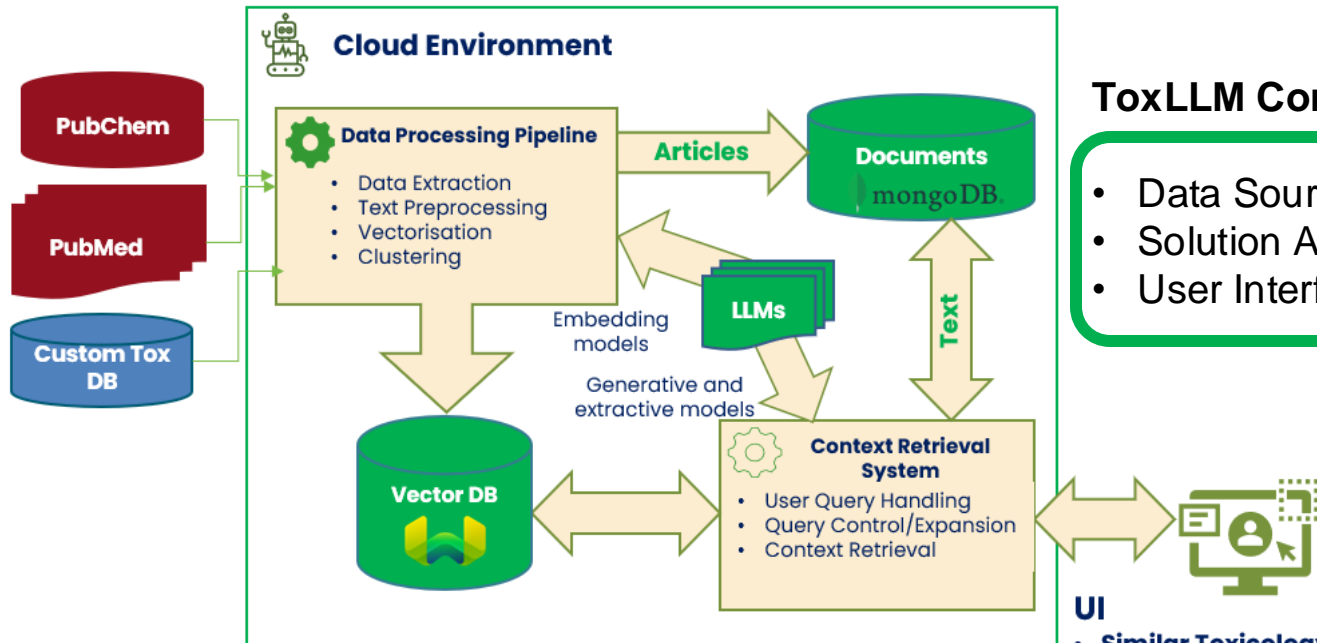
# FAIR Knowledge Infrastructure (EU-ToxRisk example)



Graph (Multiple Compounds)



<https://risk-hunt3r.net/>



## ToxLLM Components:

- Data Sources & Processing Pipelines
- Solution Architecture
- User Interface

### Colour code:

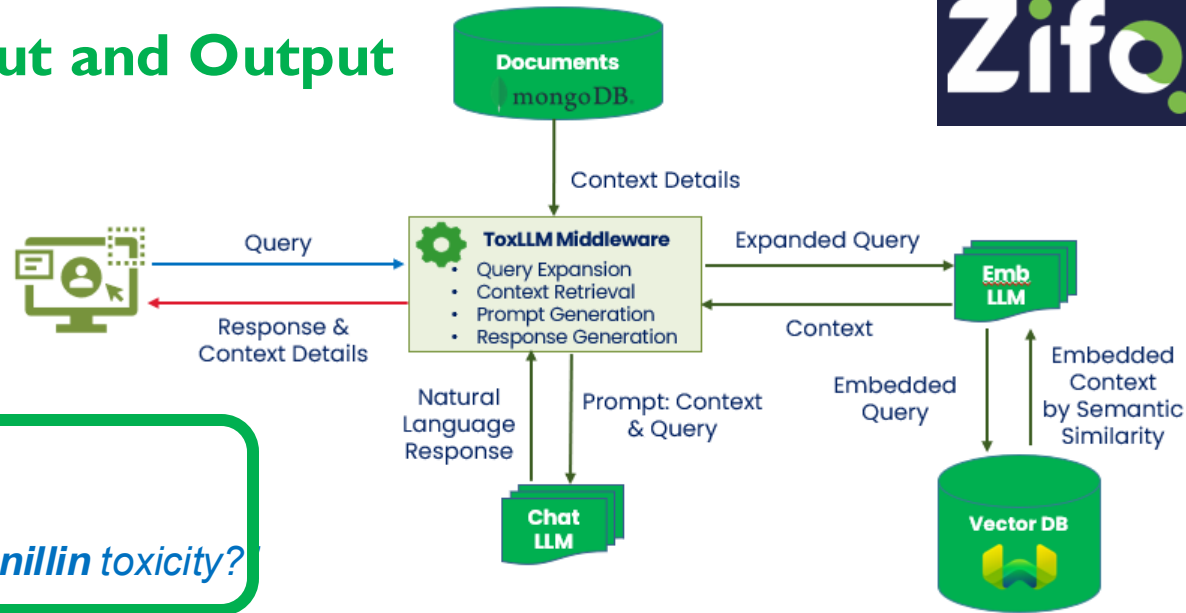
- Blue – client data/solutions
- Green – Zifo solutions
- Red – Public domain / Open-Source solutions

### UI

- Similar Toxicology Profile Search
- Generative/Extractive AI



# Context Intelligent Input and Output



## Input:

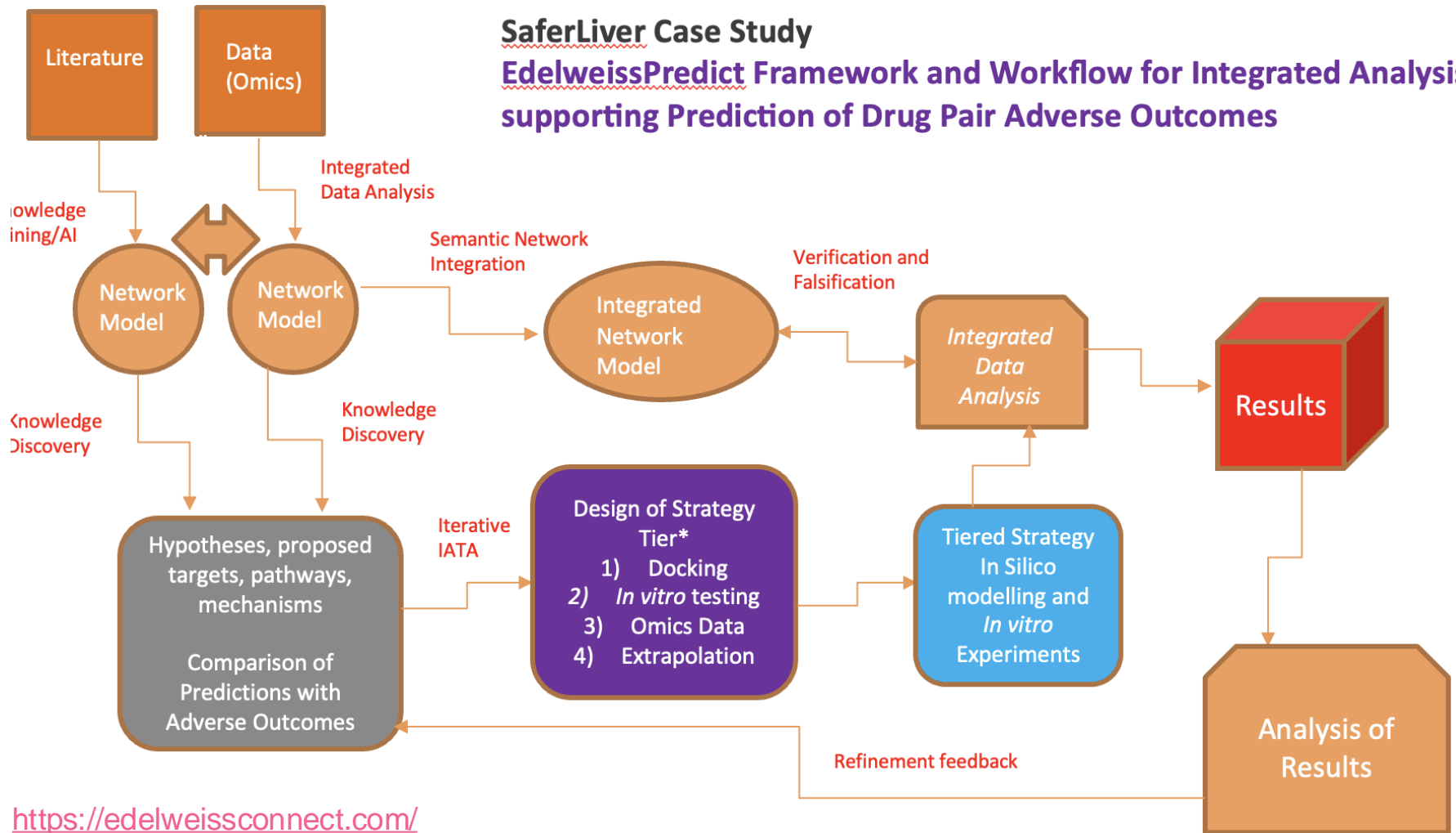
- Natural Language Query  
*“What do you know about **Vanillin** toxicity?”*

## Output:

- Natural Language Response based on query and context plus context details (references and links)  
*“Based on the provided context, here is a concise answer summarizing every piece of information:  
Vanillin is a widely used flavoring agent and fragrance ingredient that has been found to be non-toxic in most studies. However, high doses (>64 mg/kg body weight/day for 10 weeks) can cause growth depression and...”*

# SaferLiver Case Study

## EdelweissPredict Framework and Workflow for Integrated Analysis supporting Prediction of Drug Pair Adverse Outcomes



# Product knowledge base (SmartSafety) – processing documents, generating reports in formulations and ingredients

AI assist on processing and extracting information from documents into ingredient and formulation profiles

The screenshot shows the SmartSafety web application interface. At the top, there is a navigation bar with the following tabs: "Formulas", "Raw Ingredient", "Sub Ingredient", and "Contaminants". The main content area displays a product profile for "AVOCADO OIL-PRESERVED" (ID: 0033). Below the product name, there are tabs for "Properties", "Composition", "MOS" (selected), "Reports", "Testing", and "Similarity". Under the "MOS Calculation" section, there are input fields for "Product type", "Body weight" (set to 60), "Grams applied/day", and "Skin retention factor". Below this is a table with the following columns: "SI Code / Description", "Total weight", "CAS#", "EINCS#", "Skin Reten.", "Dermal Penetr.", "Daily Exposure", "Systemic Exp.", "NOAEL", and "MOS".

SI Code / Description	Total weight	CAS#	EINCS#	Skin Reten.	Dermal Penetr.	Daily Exposure	Systemic Exp.	NOAEL	MOS
1 test sub ingred...	NaN%	1			1			1	
008	0%	77-92-9			100			500	

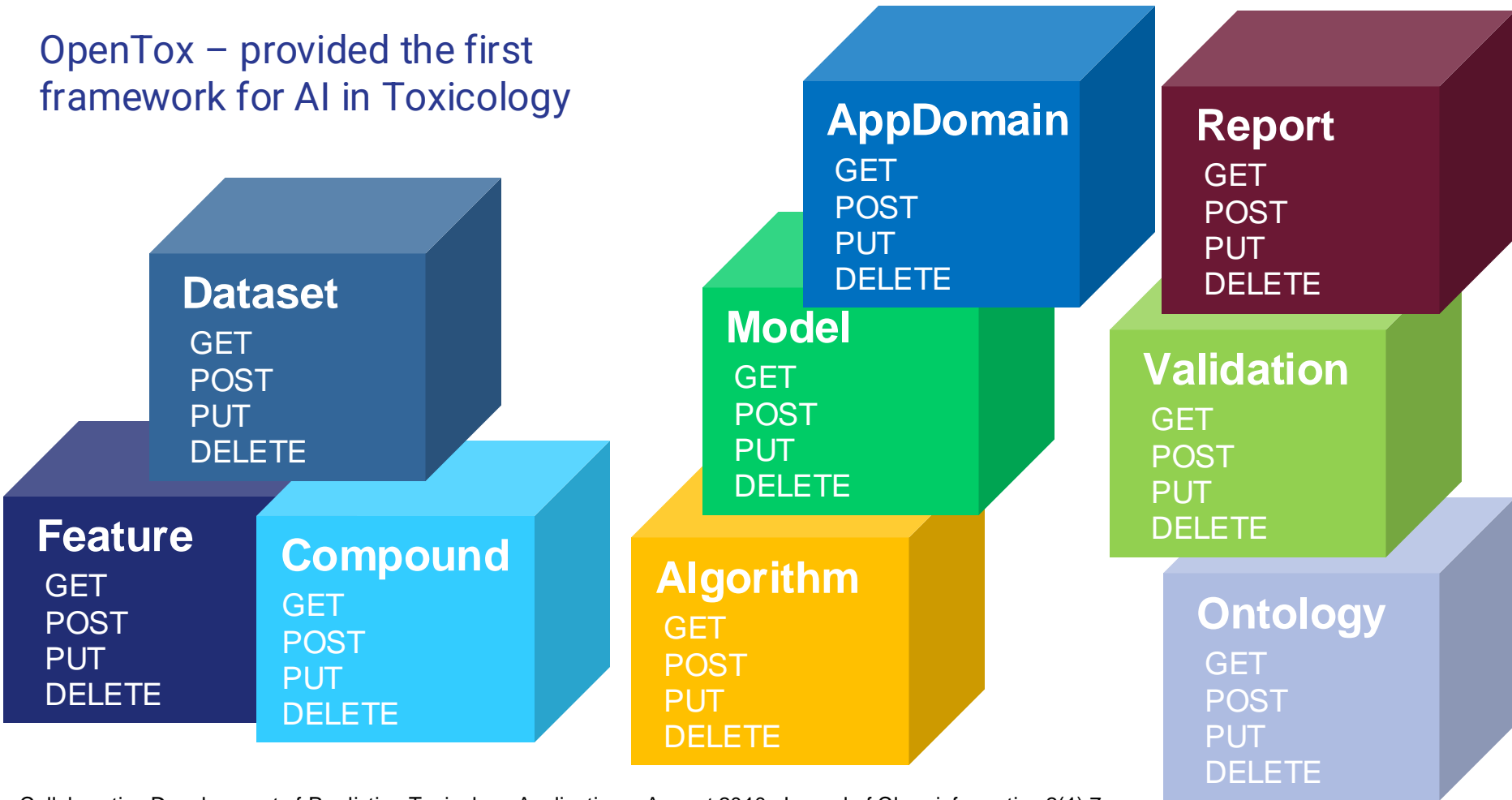
AI assist on generating reports (e.g., batches responding to a new or modified regulation)

Human – AI collaboration e.g, on curation, interpretation

<https://smartsafety.edelweissconnect.com/>

# 04 Practices and Standards

OpenTox – provided the first framework for AI in Toxicology



# Method Documentation (ToxTemp)

The screenshot shows a web browser window displaying the 'Add a new test method' page in the ToxTemp application. The browser address bar shows 'http://localhost:8080/test-methods/new/'. The page header includes the 'RISK HUNT3R' logo and a user greeting 'Welcome, tanja.burgler@bmi.bund.de'. A breadcrumb trail reads 'Home > Test Methods > Add a new test method'. The main content area is titled 'Add a new test method' and contains an introductory paragraph and a note about the form's structure. A left-hand sidebar lists 10 sections for navigation, with '1 Overview' currently selected. Below the sidebar, there are controls to 'Show fields per completeness' with a color-coded legend for 'All', 'Basic', 'Level 1', 'Level 2', and 'Level 3'. The main form area is divided into sections: '1. Overview' with a '1.1 Descriptive full-text title' field containing the text 'Toxicological test title' and 'Descriptive full-text title', and a '1.2 Abstract' field with a list of questions to guide the user. At the bottom right of the form, there are two buttons: 'Save test method' (green) and 'Cancel' (red).

Sections

- 1 Overview
- 2 General information
- 3 Description of general features of the test system/exposed
- 4 Definition of the test system as used in the method
- 5 Test method exposure substance and endpoints
- 6 Handling details of the test method
- 7 Data management
- 8 Prediction model and toxicological application
- 9 Publication / validation status
- 10 Test method transferability
- 11 Safety, ethics and specific requirements

Show fields per completeness

- All
- Basic
- Level 1
- Level 2
- Level 3

Welcome, tanja.burgler@bmi.bund.de

Home > Test Methods > Add a new test method

## Add a new test method

This form is to be used to document the status of test systems and test methods; moreover, it is intended to provide guidance for considerations around the use of test systems (or data therefrom) beyond the developer's lab; the material will constitute a form of extended SOI, containing also elements important for test method transfer within the project, or within the commercialization taskforce. Information is structured to provide an overview to interested stakeholders or to prepare for test (pre-)validation.

**Note:** This submission form is divided into eleven sections. Please refer to the [Background information / glossary](#) before filling the form.

### 1. Overview

#### 1.1 Descriptive full-text title

Provide a descriptive title using normal language without technical terms or acronyms.

How to write a title: [Toxicological test title](#)

Descriptive full-text title

#### 1.2 Abstract

Please describe in not more than 200 words the following:

- Which toxicological target (organ, tissue, physiological/biochemical function, etc.) is measured? (B.1)
- Which test system and model(s) are used? (A.1 and A.2)
- Which biological processes (e.g. receptor activation, differentiation) and / or biological events (e.g. oxidative stress, cell death) are measured / reflected by your test method? (B.2)
- To which (human) adverse outcome(s) is your test method related or could be related? (B.3, B.2 and B.2)
- Which (candidate) drug(s) your test method (potentially) predict? (B.7 and B.8)
- Does the test method capture an endpoint of current regulatory studies? (B.9)
- If the method has undergone some form of validation / evaluation, give its status. (B.4)

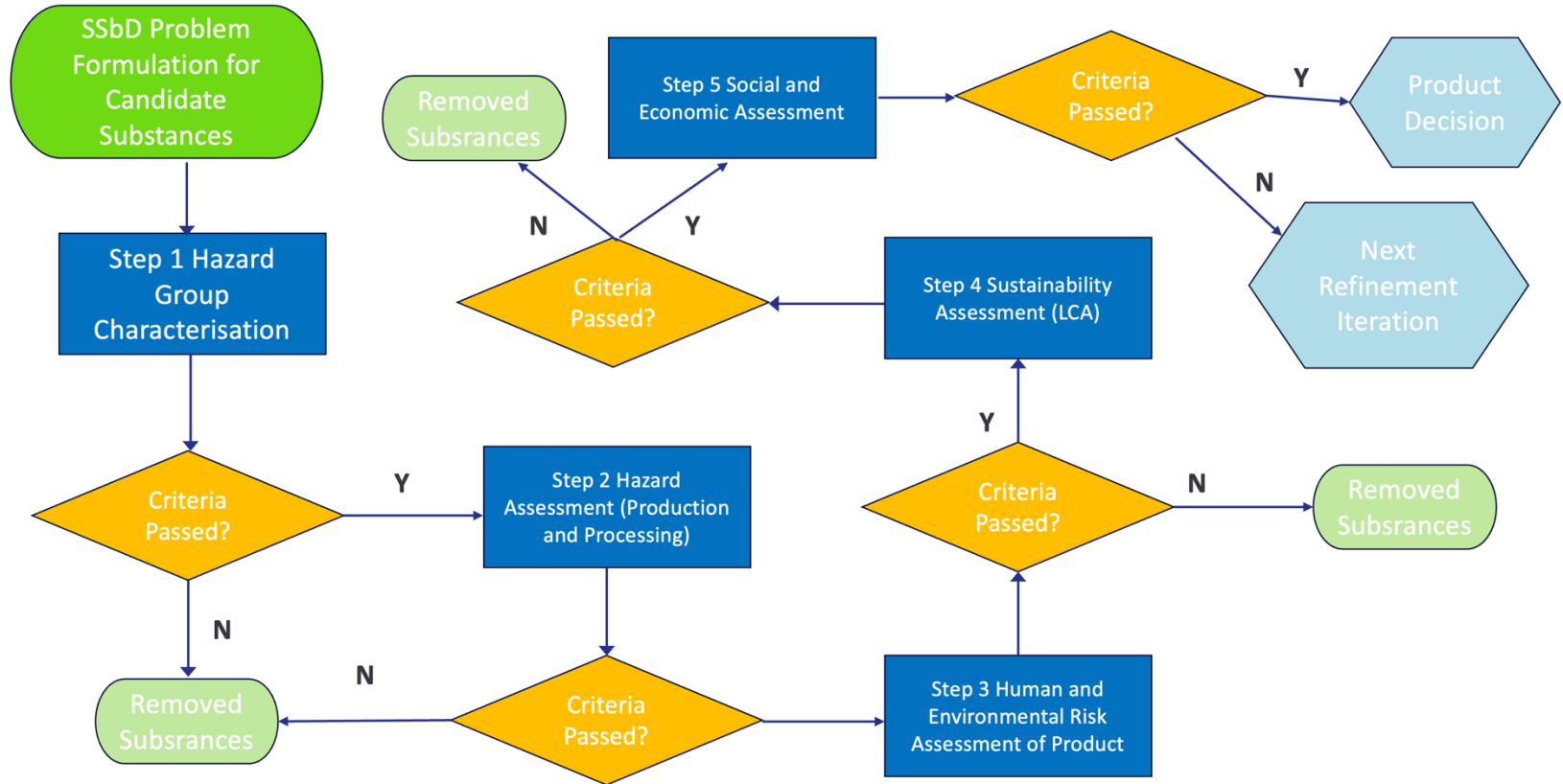
Note: the sections should give an overview. Further use for search in the registration database, as indicated by 'human's relevance'

Abstract

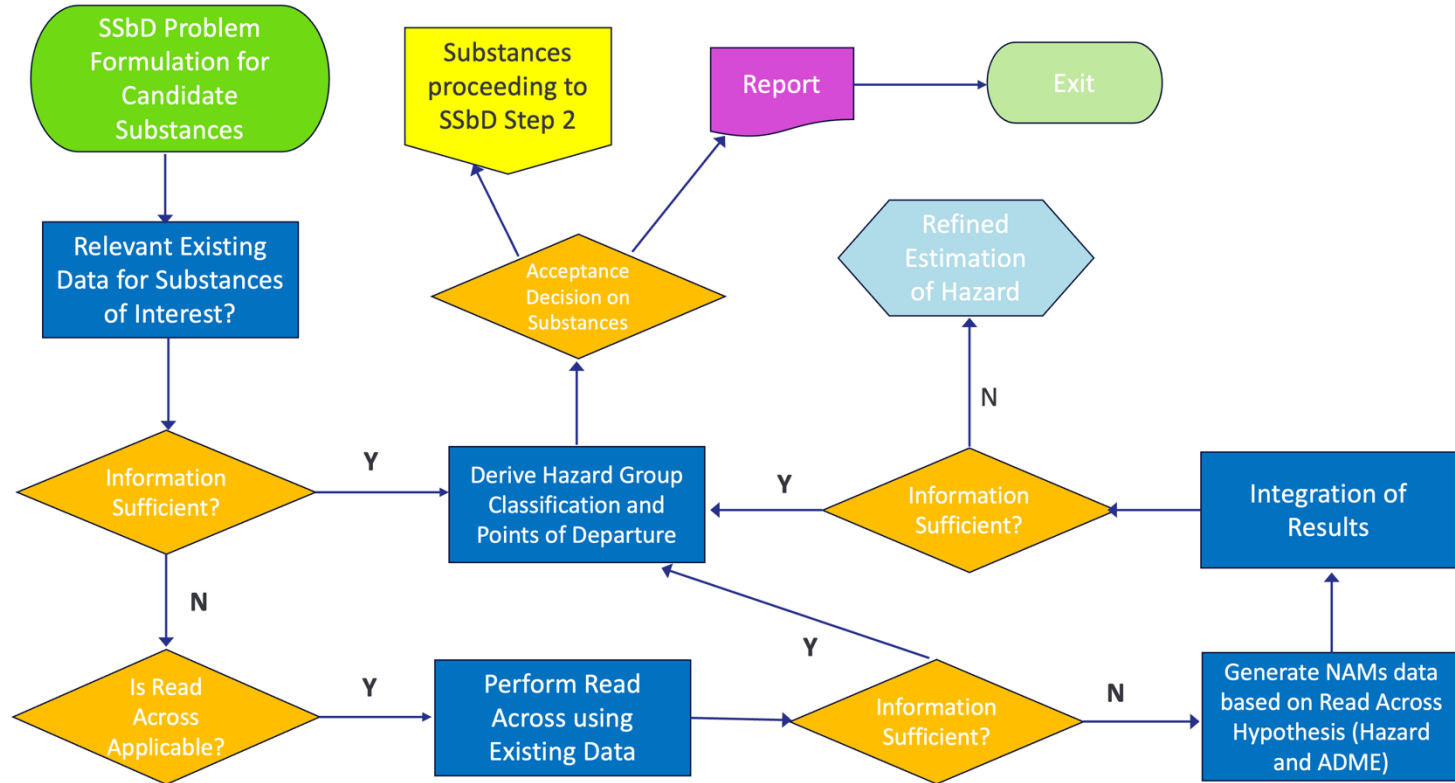
Save test method Cancel

Template for the description of cell-based toxicological test methods to allow evaluation and regulatory use of the data, Alice Krebs et al (2019). <https://www.altex.org/index.php/altex/article/view/1433>

# Workflows (Safer and Sustainable by Design (SSbD))

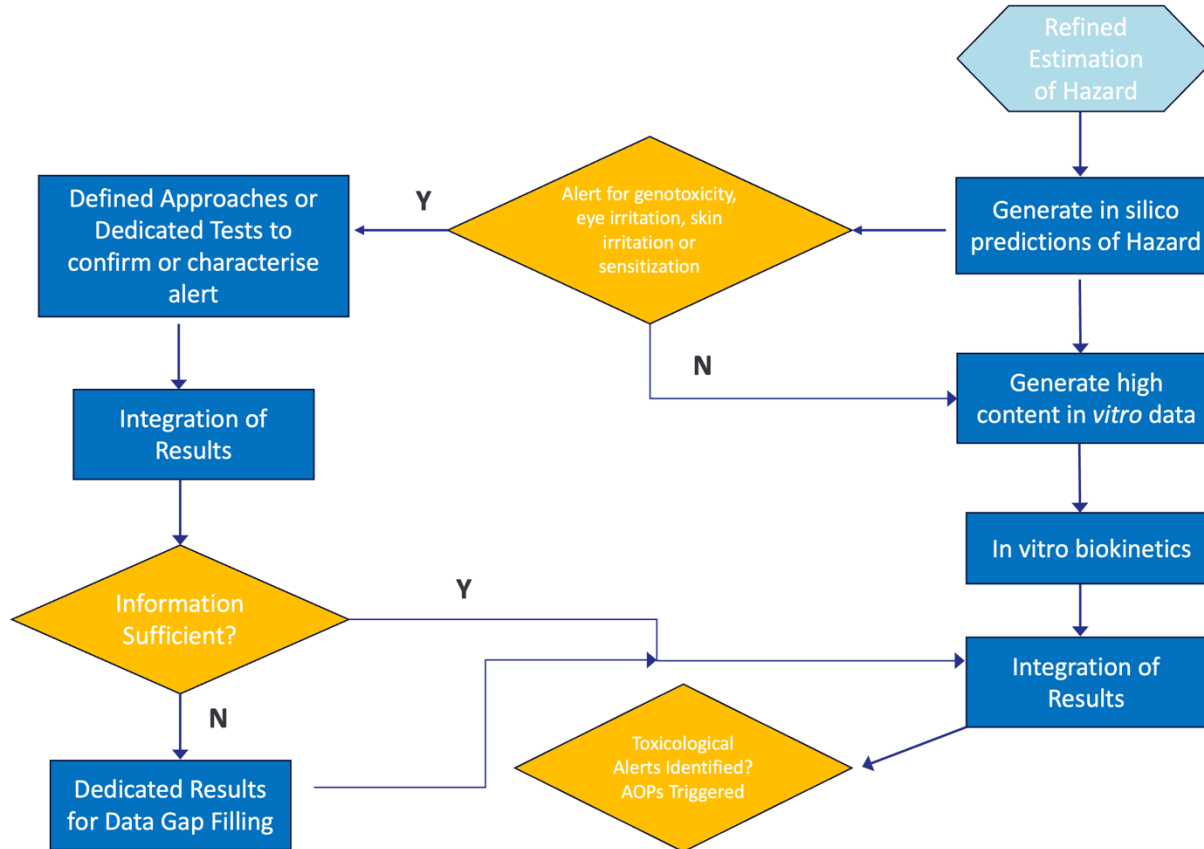


# Workflows (SSbD Step 1)





# Workflows (hazard refinement)



# Incorporating data on FAIR Models into our NGRA Knowledge Infrastructure

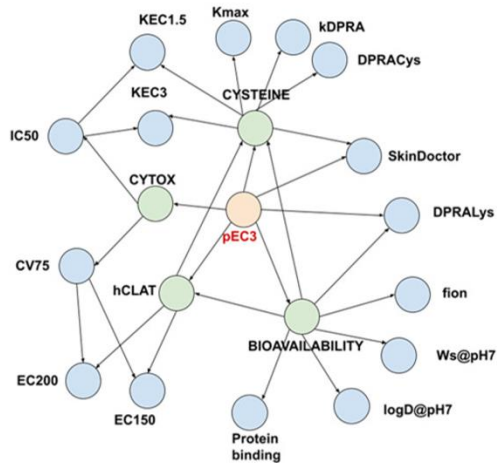
- *In silico* models are used widely to support Next Generation Risk Assessment (NGRA).
- *In silico* models for NGRA must be findable and reproducible.
- FAIR principles have been applied to *in silico* models for chemical risk assessment.
- 18 FAIR principles for *in silico* models are proposed.
- FAIRification of *in silico* models is intended to increase use and acceptance.

Mark T.D. Cronin, Samuel J. Belfield, Katharine A. Briggs, Steven J. Enoch, James W. Firman, Markus Frericks, Clare Garrard, Peter H. Maccallum, Judith C. Madden, Manuel Pastor, Ferran Sanz, Inari Soininen, Despoina Sousoni

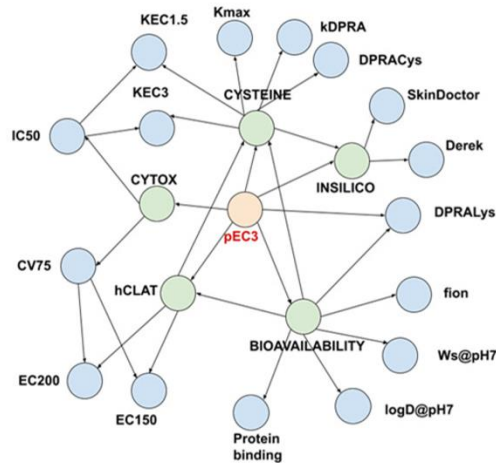
Making *in silico* predictive models for toxicology FAIR, Regulatory Toxicology and Pharmacology, Volume 140, 2023, 105385, ISSN 0273-2300, <https://doi.org/10.1016/j.yrtph.2023.105385>.  
(<https://www.sciencedirect.com/science/article/pii/S0273230023000533>)

# Weight of Evidence (Bayesian Networks)

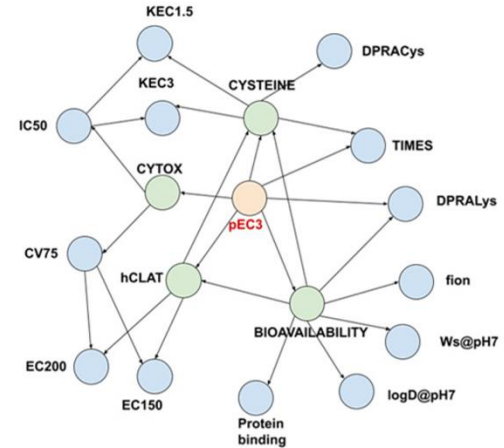
## Model A



## Model B



## SaferSkin-BN (baseline)



SaferSkin example implementing Defined Approach with Beiersdorf (2024)

<https://www.mdpi.com/2305-6304/12/9/666>

# 05 Legal and Ethics

# Alignment with Legislation, DESIGN FOR AI-SAFETY (CBRN)

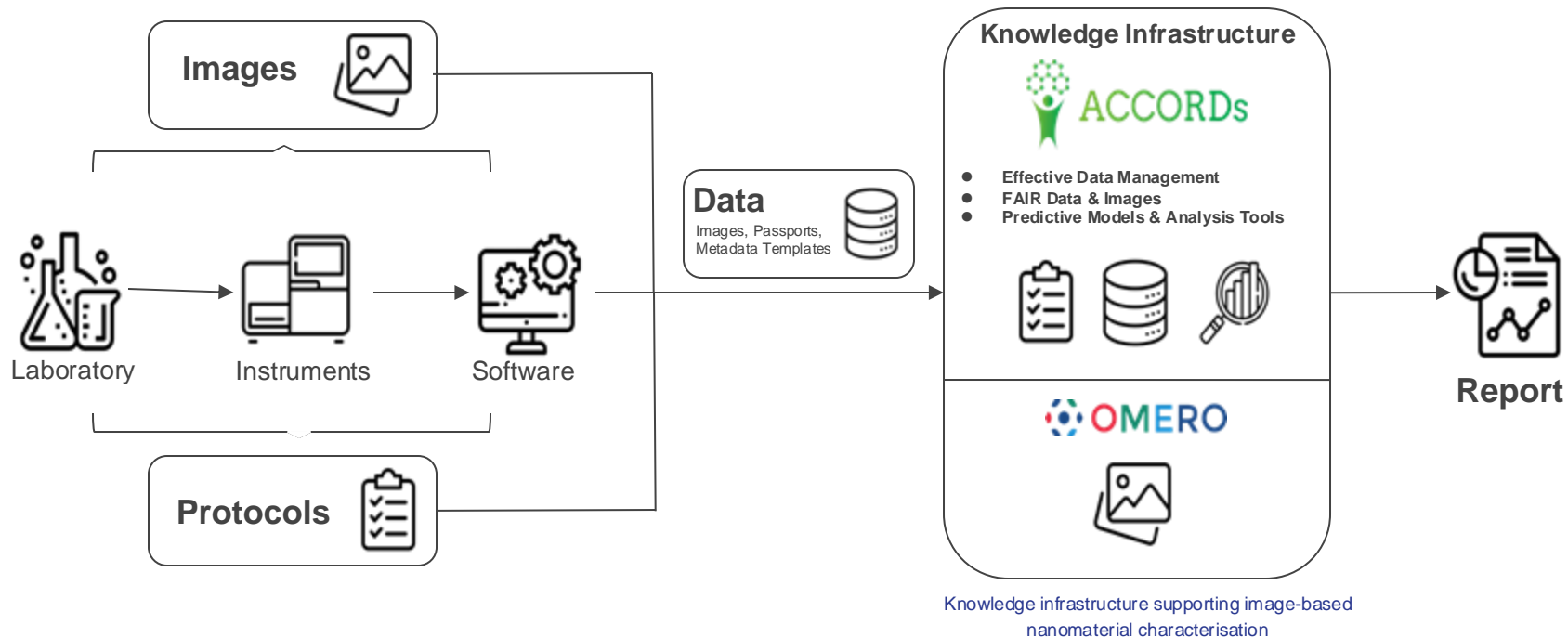
- Comply with AI safety regulations
  - NIST AI Risk Management Framework
  - EU AI Act
- Prevent misuse in context of CBRN threats (Chemical, Biological, Radiological, and Nuclear).
- We analyse how AI safety measures impact our use cases.

## OpenAI Example



# 06 (FAIR) Use Case Example

# Characterisation workflow



# Image related data in ACCORDs Image Repository (OMERO)



Easy figure creation  
for publication



Organised folder  
structure

The screenshot displays the OMERO web interface. On the left, a tree view shows a hierarchical folder structure under 'ACCORDs 14'. The main area is a grid of image thumbnails, with one selected and highlighted in blue. On the right, a 'General' metadata panel is visible, showing details for the image '1\_20230413pm0250.bmp', including its ID (4097), owner (Pascal Avdi), and acquisition details like dimensions (1024 x 1024) and channels (Red, Green, Blue).



Data and metadata  
overview



Analysis, Editing etc.

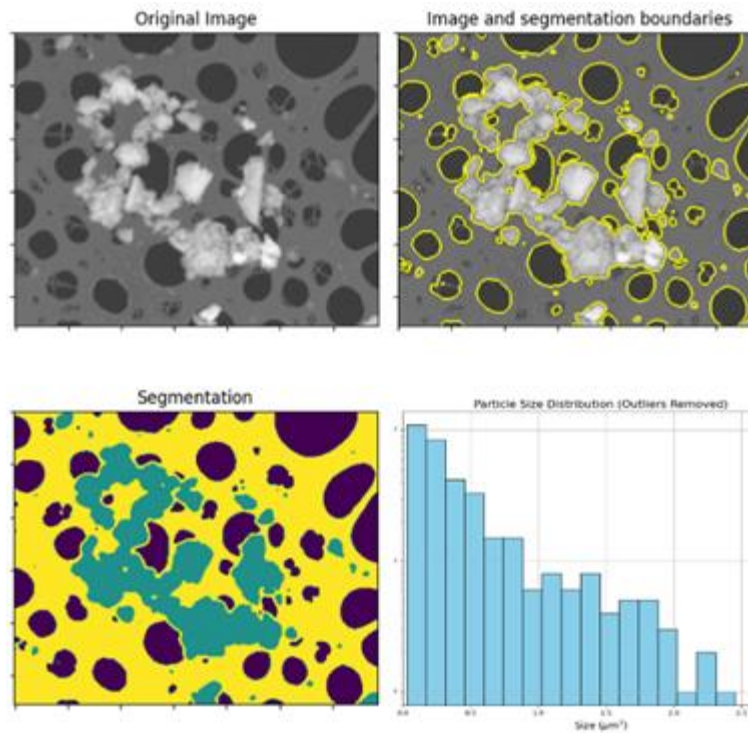
<https://accordsproject.com/>



# Automated Metadata Extraction, Image Annotation and Analysis

## OME-Formats for FAIR Images

With image conversion to OME-TIFF and OME-XML we can annotate customised metadata to images and image data sets in an open format supporting FAIR goals



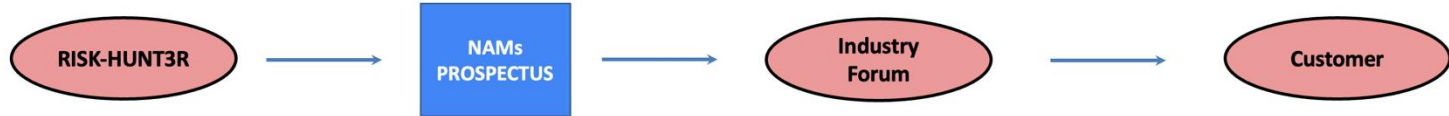
# 07 Outlook

# Tackling Challenges

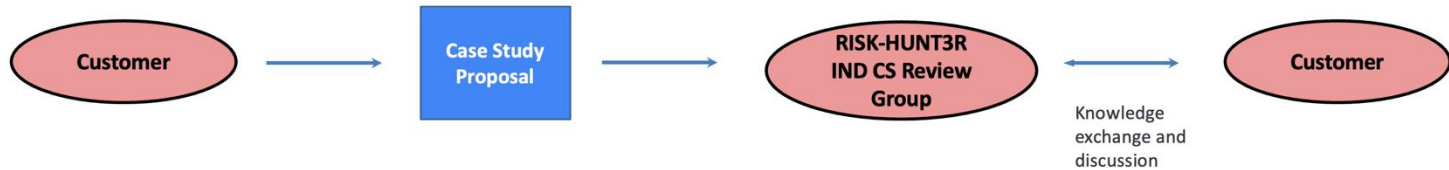
## IND Case Study Process Overview



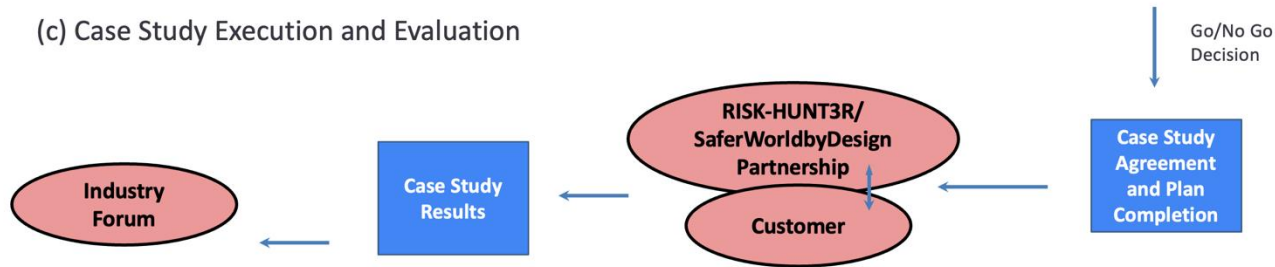
(a) Background Knowledge Sharing



(b) Case Study Development



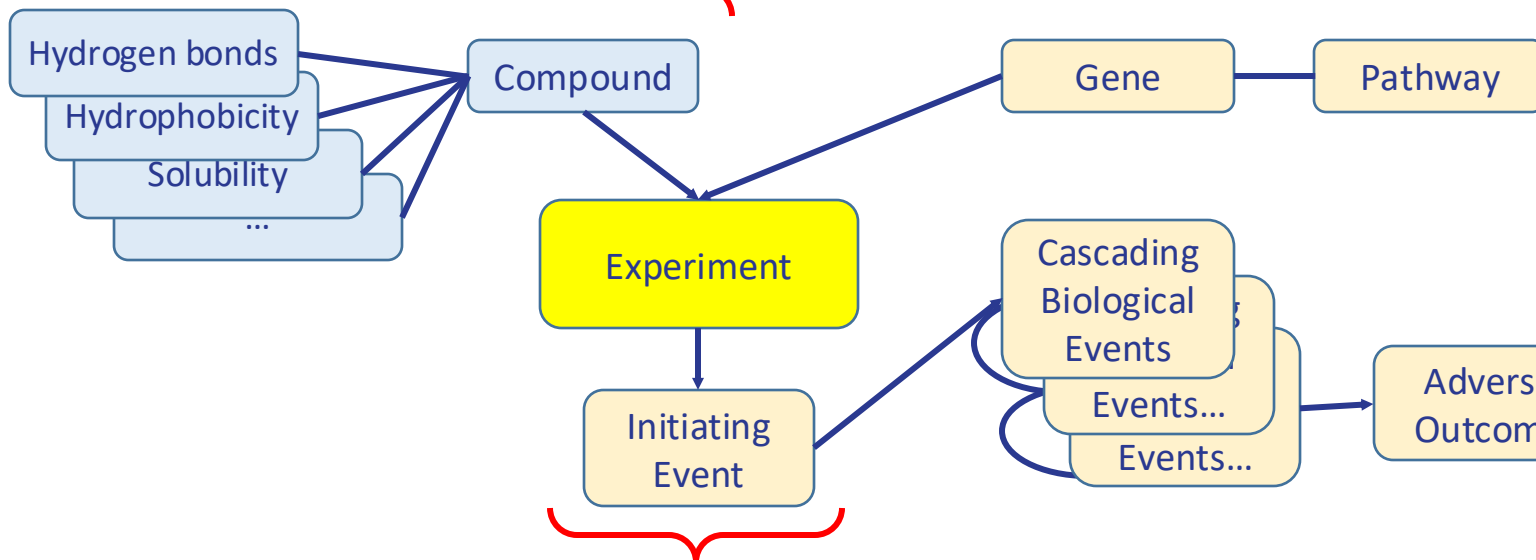
(c) Case Study Execution and Evaluation



Sharing of lessons learned and best practices

# Integration of Chemical and Biological Information, Testing of Models, Knowledge Graphs and AI-Assisted workflows

**Compound properties support read across**



**Experimental details provide context**

**Linked biological events predict adverse outcomes**

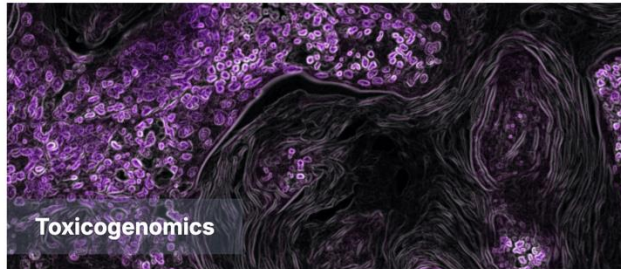
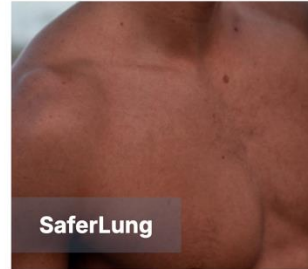
# Integrated Solution Development



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## SaferWorldbyDesign Solutions



<https://saferworldbydesign.com/>

## We strive for collaborative innovation working with stakeholders!

At Edelweiss Connect, we foster creativity, collaboration, and curiosity to drive continuous improvement in risk assessment and data management. By maintaining an agile and adaptive mindset, we navigate challenges, refine ideas, and explore new frontiers to provide solutions in safe design, risk assessment and sustainability.

<https://www.edelweissconnect.com/>

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