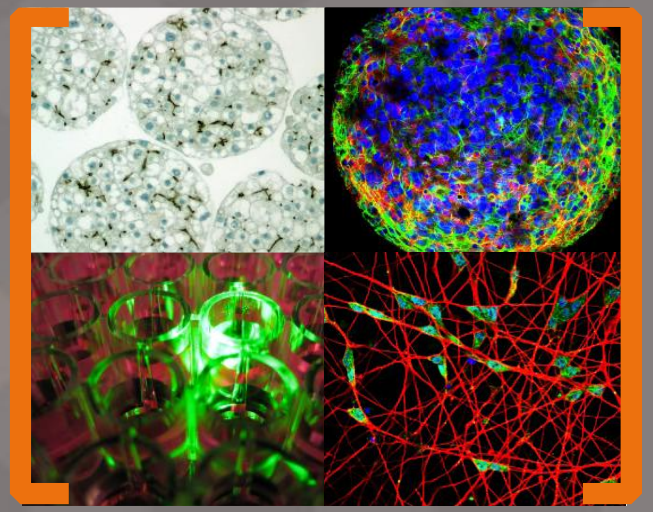
EU-ToxRisk Final Symposium

3-4 November 2021

How has EU-ToxRisk impacted on innovative science research outreach?

Thomas Steger-Hartmann
EU-ToxRisk SAB chair
Bayer
Germany



A few thoughts on the role of an SAB

(members: H. Appelgren, T. Heinonen, D. Knight, R. Paules, M. Sachana, M. Schwarz, R. Thomas, W. Tong, J. W. van der Laan)

- If the vision is "… to drive the required paradigm shift in toxicological testing away from 'black box' animal testing towards a toxicological assessment based on human cell responses and a comprehensive mechanistic understanding", then this is not only a scientific challenge, but requires broad stakeholder engagement.
- Terms of Reference (April 26th, 2016)

Objectives of the SAB

1) The SAB will provide independent expert feedback and recommendations on project progress and plans, and facilitate bridging to stakeholder groups outside the Consortium, contribute their experiences, and cooperate to ensure that the project:

a) remains at the forefront of the state-of-the-art
b) meets the highest scientific and ethical standards
c) promotes clear and open communication that allows dissemination, uptake and exploitation of results
d) permits bridging to other ongoing initiatives and regulatory bodies in Europe and the world

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Getting regulatory stakeholders involved

Dr Jean-Marc Vidal
Clinical Pharmacology and Non-clinical Support Service
Safety Working Party (Human medicines) scientific secretariat
Specialised Scientific Disciplines Department
European Medicines Agency
30 Churchill Place
Canary Wharf, London E14 5EU
United Kingdom

Dr Hubert Deluyker
Scientific Adviser to the Executive Director
European Food Safety Authority
Via Carlo Magno 1/A
I-43126 Parma
Italy

Berlin, August 3rd, 2016

Introduction of EU-ToxRisk to EMA and invitation for co-operation

Dear Dr Vidal,

I am writing to you in my capacity of chair of the Scientific Advisory Board (SAB) of the EU-ToxRisk project. My colleague on the SAB, Jan Willem van der Laan of the Medicines Evaluation Board in the Netherlands, has encouraged us to contact EMA for a potential cooperation with EU-ToxRisk.

Let me briefly introduce the project: the six-year EU-ToxRisk project (http://www.eu-toxrisk.eu/), which was launched this January as a seamless follow up of the SEURAT-1 project (http://www.seurat-1.eu/), is a

Berlin, August 1st, 2016

Introduction of EU-ToxRisk to EFSA and invitation for co-operation

Dear Dr Deluyker,

I am writing to you in my capacity of chair of the Scientific Advisory Board (SAB) of the EU-ToxRisk project. My colleague on the SAB, Derek Knight of ECHA, has encouraged us to contact EFSA because EU-ToxRisk follows up on SEURAT-1, which EFSA took an interest in.

The six-year EU-ToxRisk project (http://www.eu-toxrisk.eu/), which was launched this January as a seamless follow up of the SEURAT-1 project (http://www.seurat-1.eu/), is a €30 million H2020-supported

Dr Watze de Wolf
Chair of the Member State Committee
Committees Secretariat Regulatory Affairs
European Chemicals Agency
Annankatu 18, P.O. Box 400
FI-00121 Helsinki
Finland

Berlin, August 1st, 2016

Introduction of EU-ToxRisk to the MSC and invitation for co-operation

Dear Dr Watze de Wolf,

I am writing to you in my capacity of chair of the Scientific Advisory Board (SAB) of the EU-ToxRisk project. My colleague on the SAB, Derek Knight of ECHA, has encouraged us to contact ECHA's Member State Committee (MSC) to seek volunteers from the members for collaborating with EU-ToxRisk.

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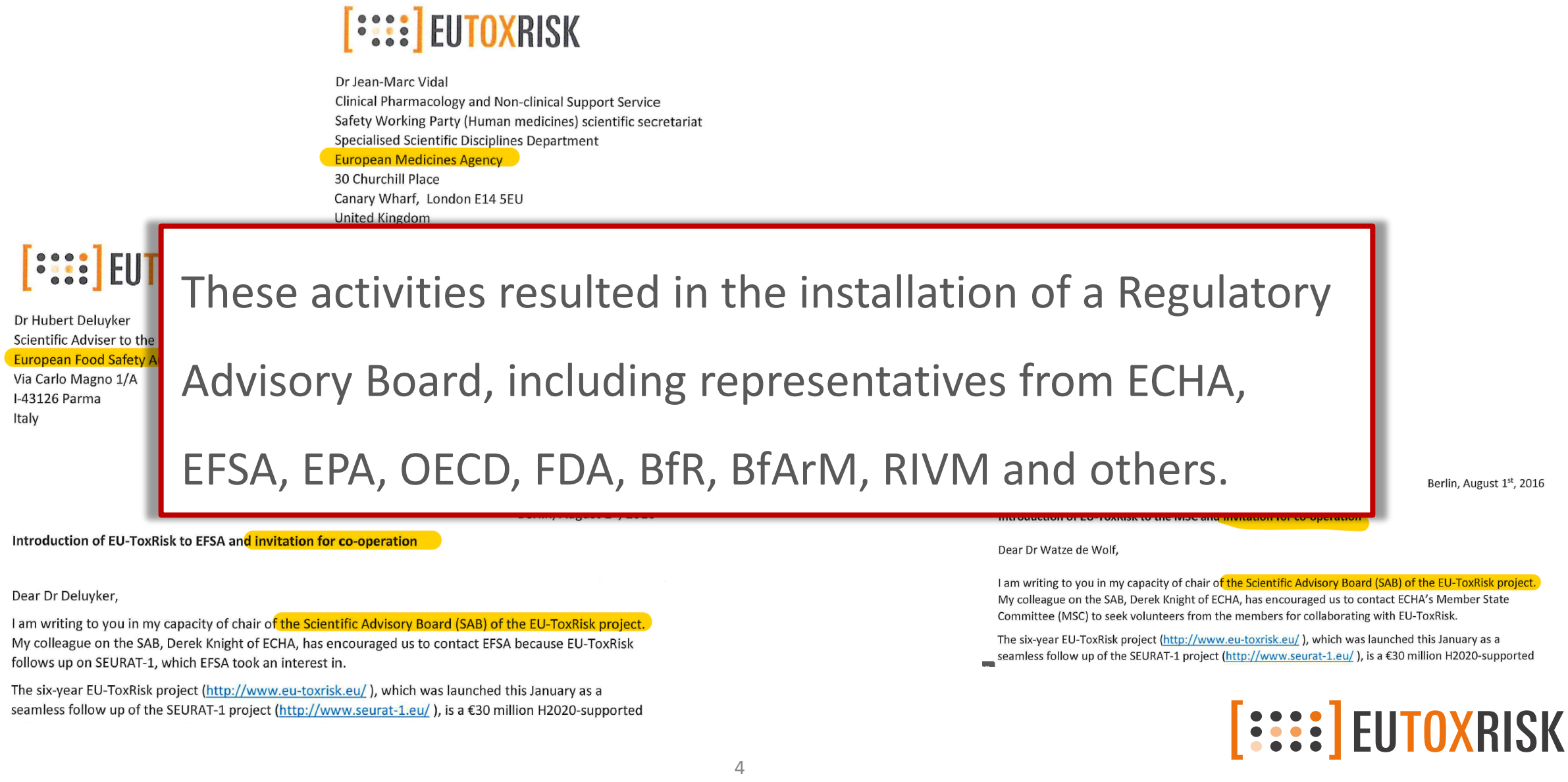
Regulatory stakeholder involvement has impacted innovative science

(EFSA, EMA, ECHA, …)



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These activities resulted in the installation of a Regulatory Advisory Board, including representatives from ECHA, EFSA, EPA, OECD, FDA, BfR, BfArM, RIVM and others.

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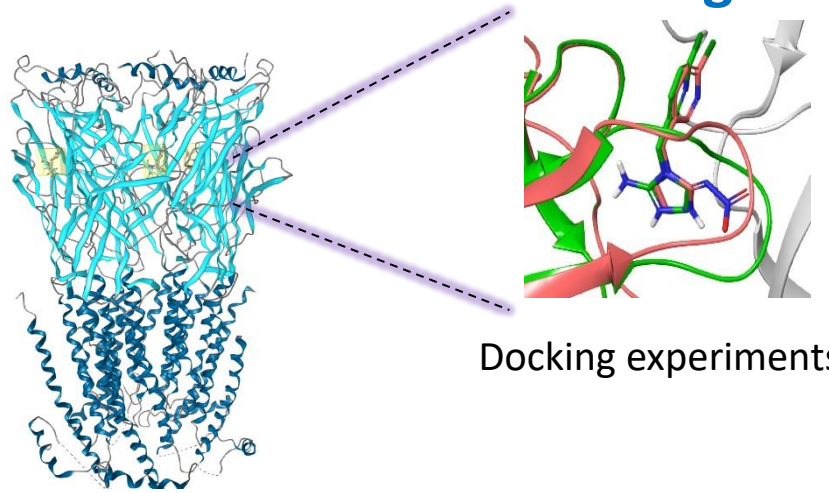
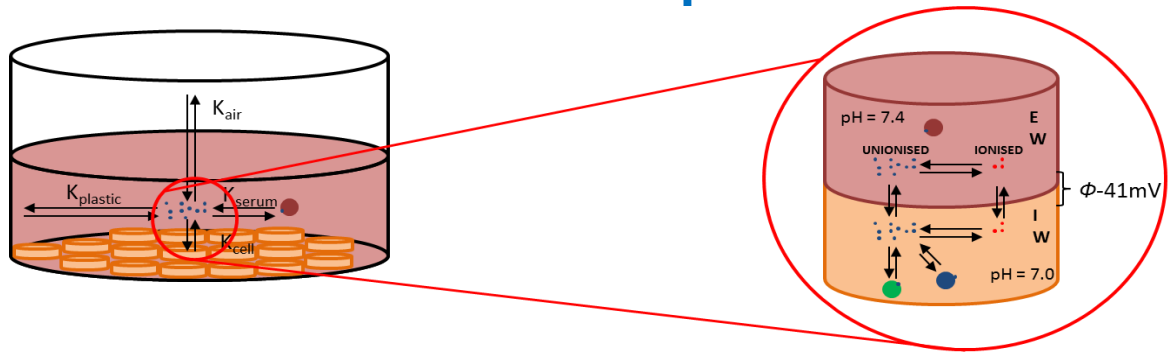
Enlarging the toolbox: development of novel *in silico* approaches

Structural modelling

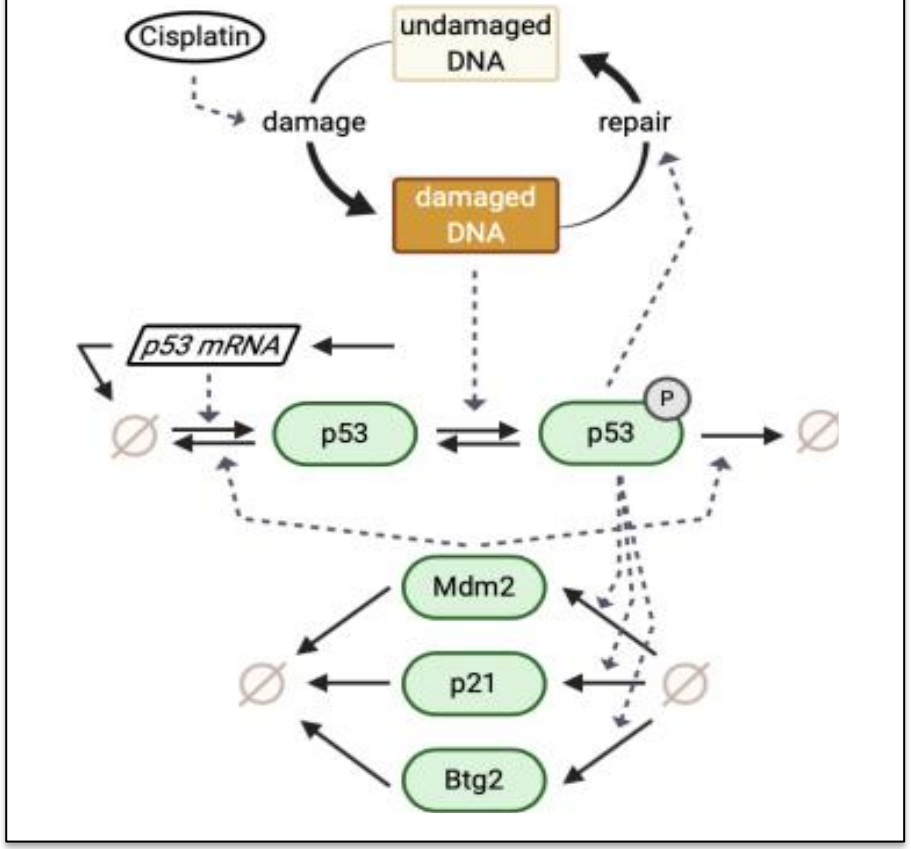


Docking experiments

Virtual *in vitro* cell disposition model



Computational biology - qAOP



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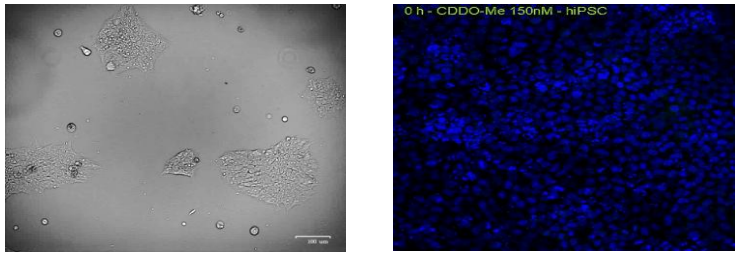
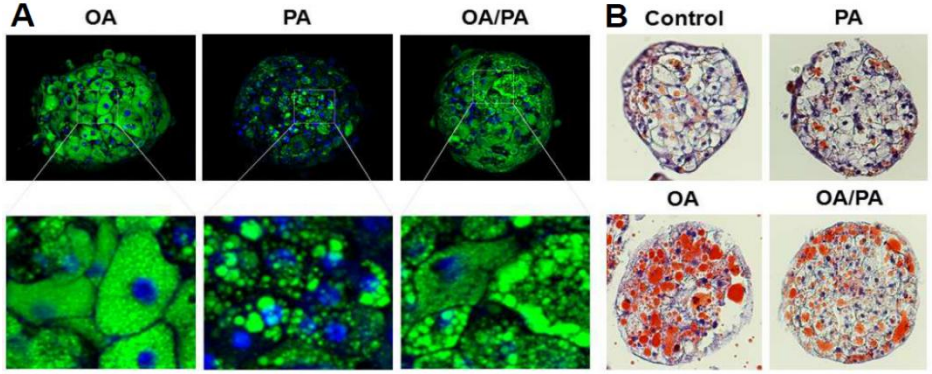
Enlarging the toolbox: development of advanced *in vitro* approaches

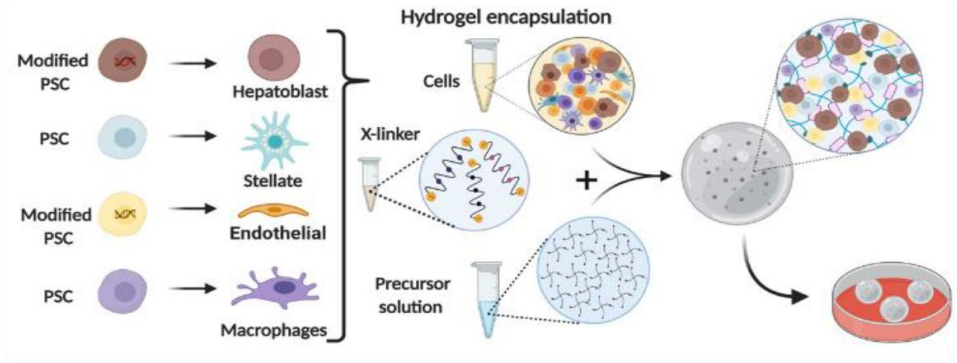
CRISPR-based fluorescent reporters in stem cells



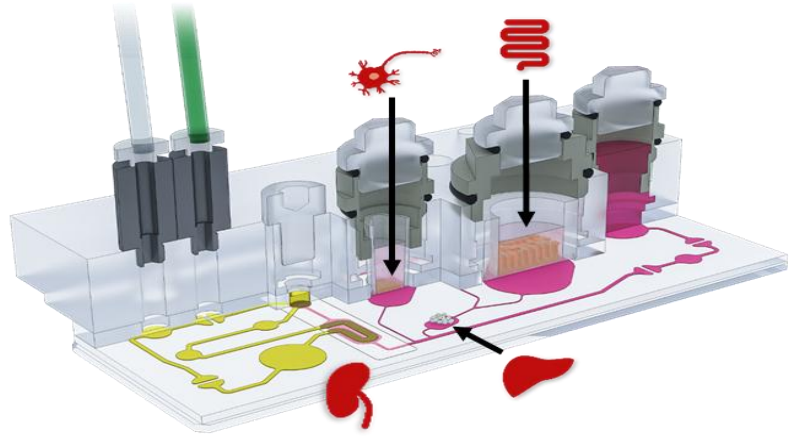
Diseased liver microtissues



Stem cell-derived multi-cell model



Four-organ-chip



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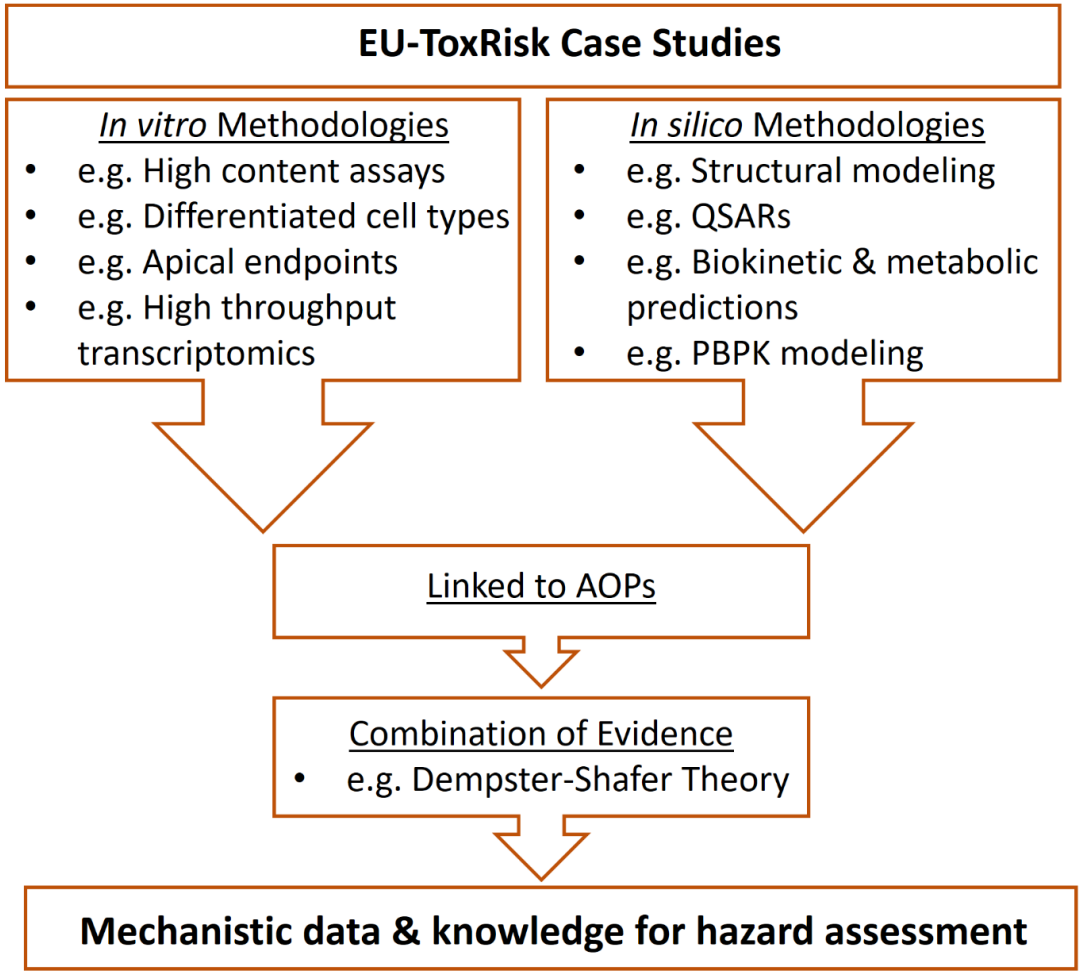
Integration components of the toolbox into Case Studies

The first set of Case Studies focused on regulatory application for NAM-supported read-across and provided:

- data on the predictivity of the EU-ToxRisk battery of human-relevant *in vitro* systems for different human toxicity endpoints
- insight into kinetic behavior
- likelihood of activation of Key Events (KEs) or Adverse Outcomes (AOs).



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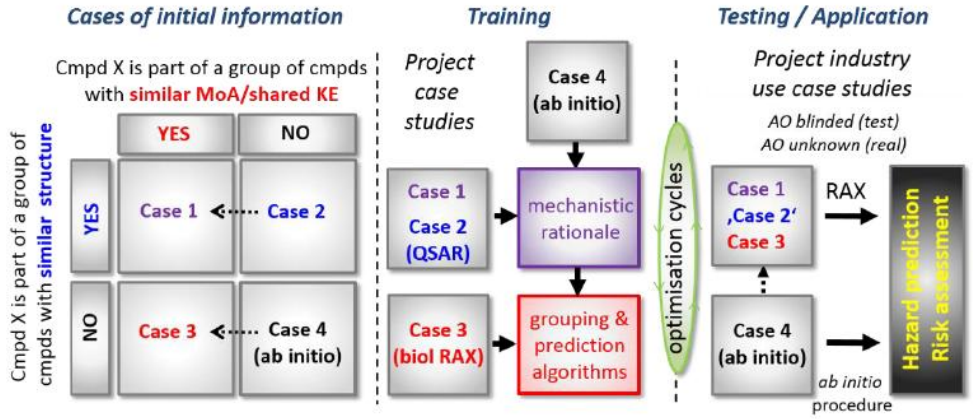
From case studies to risk assessment

14 **case studies**, including 3 industry-joint case studies

5 **reports published in the OECD** Environment, Health and Safety Publications Series on Testing

1 **PARERE consultation**: Preliminary As Relevance of EUToxRisk's NAMs

4 **OECD IATA Case Studies subm** neurotoxicity



Research Article

New Approach Methods (NAMs) Supporting Read-Across: Two Neurotoxicity AOP-based IATA Case Studies

Wanda van der Stel[1], Giada Carta[2], Julie Eakins[3], Johannes Delp[4], Ilinca Suciu[4,5], Anna Forsby[6], Andrea Cediel-Ulloa[7], Kristina Attoff[6], Florentina Troger[8], Hennicke Kamp[9], Iain Gardner[10], Barbara Zdrazil[8], Martijn J. Moné[1], Gerhard F. Ecker[8], Manuel Pastor[11], Jose Carlos Gómez-Tamayo[11], Andrew White[12], Erik H. J. Danen[1], Marcel Leist[4], Paul Walker[3], Paul Jennings[2], Susanne Hougaard Bennekou[13] and Bob van de Water[1]

[1]Division of Drug Discovery and Safety, Leiden Academic Centre of Drug Research, Leiden University, Leiden, The Netherlands; [2]Division of Molecular and Computational Toxicology, Department of Chemistry and Pharmaceutical Sciences, AIMMS, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [3]Cyprotex Discovery Ltd, Alderley Park, Macclesfield, Cheshire, United Kingdom; [4]Chair for In vitro Toxicology and Biomedicine, Department inaugurated by the Doerenkamp-Zbinden Foundation, University of Konstanz, Konstanz, Germany; [5]Konstanz Research School Chemical Biology, University of Konstanz, Konstanz, Germany; [6]Department of Biochemistry and Biophysics, Stockholm University, Stockholm, Sweden; [7]Department of Organismal Biology, Uppsala University, Uppsala, Sweden; [8]Department of Pharmaceutical Chemistry, University of Vienna, Vienna, Austria; [9]BASF, Ludwigshafen, Germany; [10]Certara UK Ltd, Sheffield, United Kingdom; [11]Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Spain; [12]Unilever, Bedfordshire, United Kingdom; [13]National Food Institute Technical University of Denmark (DTU), Lyngby, Denmark

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Advanced toolbox applied to case studies

Learning set of case studies

Steatosis, DART, motorneurons

Advanced set of case studies

Neurotoxicity, exotic targets, non-toxicity

Testing set of case studies

Joint industry studies

Case Study Reports „Mock Sub-missions“

Case Study Learnings

Multi-organ Metabolism
How to apply NAMs to identify chemicals whose primary repeated dose toxicity depends on multiple-organ metabolism (liver-kidney)

High Concern Toxicity Profile Screen
How to apply NAMs to identify among chemicals those with a high concern toxicity pro

Low Tox & Ab Initio Case Study
How to apply NAMs to identify low and non-toxic chemicals and to identify the toxicological profile of chemicals whose toxicity profile is completely unknown

Next-generation risk assessment (NGRA) of developmental neurotoxicity liabilities of neonicotinoid insecticides
How to apply NAM to identify DNT toxicants, and to serve as an alternative to the available in vivo *guideline study*

syngenta

Unilever

Cosmetics Europe
the personal care association

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Further outreach aspects

>27 dedicated **sessions at international conferences**

>150 **individual participations** to external events (posters, presentations)

18 **international workshops** (including 5 summer schools), with broad stakeholder engagement (e.g., Rax workshop with regulators)

>50 **PhD candidates** since the start of the project

164 **scientific publications** acknowledging the EU-ToxRisk project

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Further outreach aspects

>27 dedicated **sessions at international conferences**

>150 **individual participations** to external events (posters, presentations)

164

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Summary impact record

EU-ToxRisk …

- has developed **new in silico and in vitro tools** for safety assessment
- integrated these tools into **innovative NAMs**
- applied these NAMs in a series of **case studies jointly with industry**
- evaluated the outcome of the case studies together with **regulators**
- contributed to overcome the translational gap between animals and humans through a better reflection of the **human biology and pathophysiology in the developed NAMs**
- has promoted and increased **awareness of quality and uncertainty issues** in development and selecting of test models, methods and strategies **to achieve reproducible and relevant results**
- trained a **new generation of safety scientists**, which will contribute to changing the current testing and assessment paradigm

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This project has received funding from the European Union's **Horizon 2020** research and innovation programme under grant agreement No 681002

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www.eu-toxrisk.eu

Thank you