EU-ToxRisk : Industry Perspective

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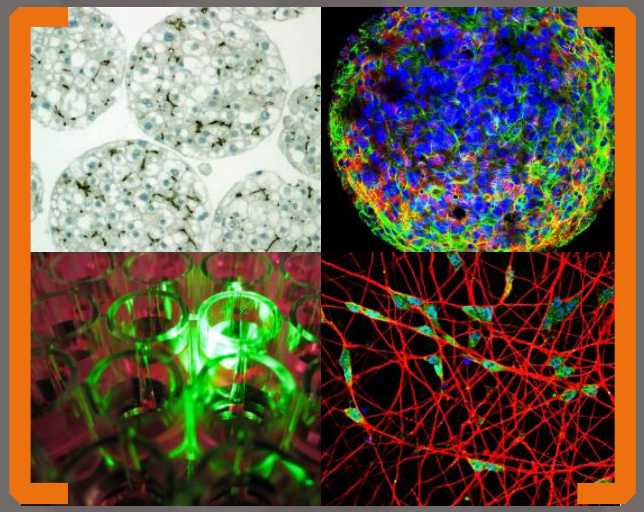
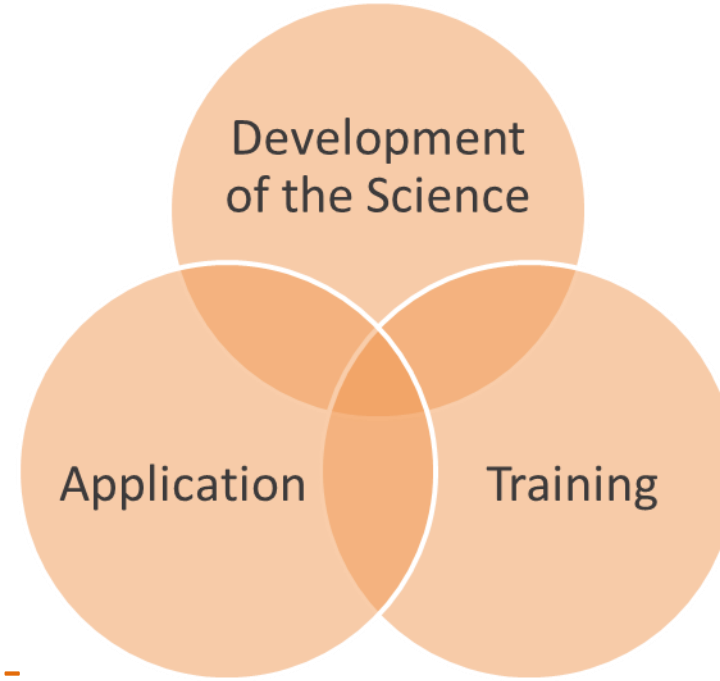


Context

- Vision – a paradigm shift in toxicology evolving the AOP mechanism based testing allow to push the entire field forward in an integrated manner,
- Define risk assessment strategies for various applications and industry sectors with different regulatory requirements.
- European Green Deal and Chemical sustainability strategy to strive for a toxic-free environment



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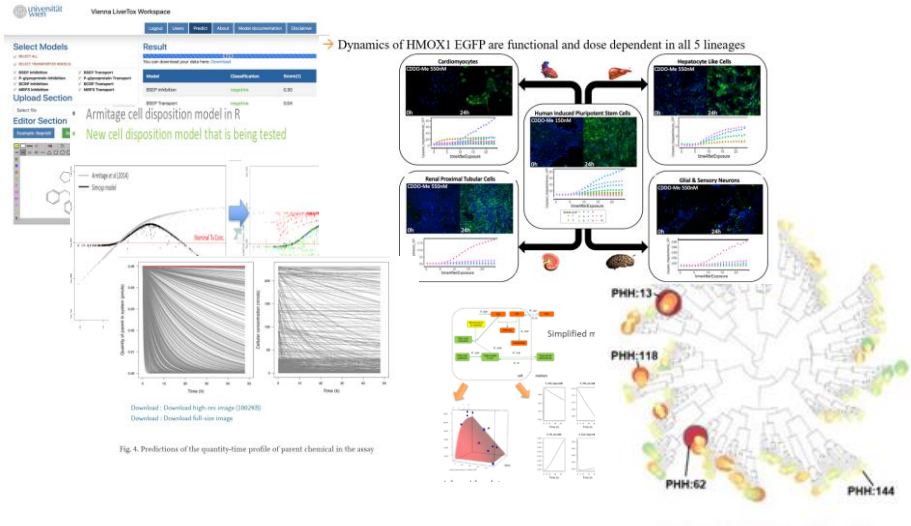
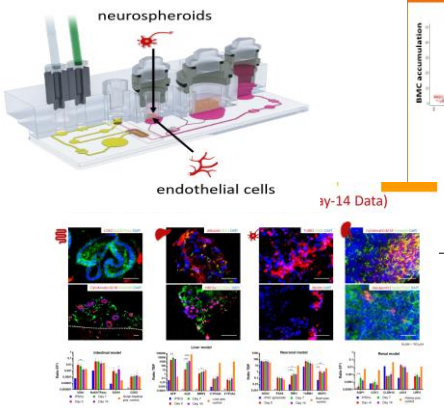
Scientific - developments

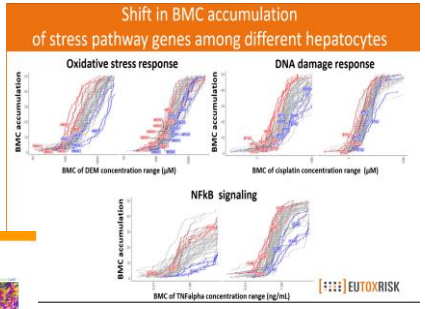
Throughput → **Complexity**

Need addressed: *Speed, cost* | *Primary, long-term, differentiated* | *Variabilities* | *Multi-organ integration* | *Human and in vivo anchoring*

Chemical Exposure	MIE	Cellular Level	Organ Level	Individual Level







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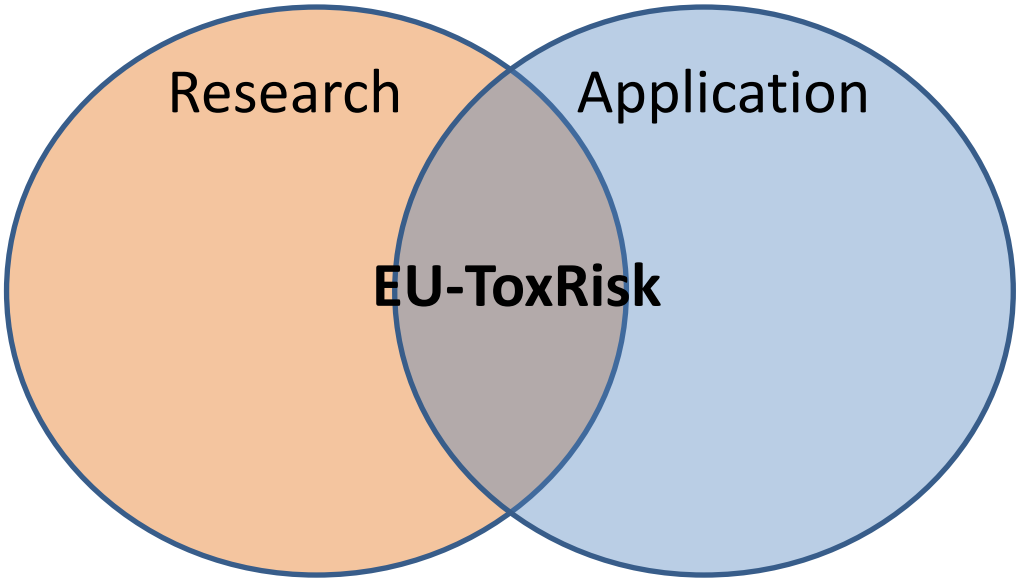
Progressing from science to application

Objective: EUToxRisk21 strategy focuses on integration of essential scientific approaches to meet both industry risk assessment need and the regulatory needs



1) deploying currently available in vitro and in silico tools as well as the development of new ones where gaps are identified
2) To test, optimize and validate the performance and practical usefulness of the IATA along case studies
3) Build agreement for regulatory acceptance in applicability domains.

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Productionisation

- Longevity of assays
- Define quality standards for assay use (eg GLP)
- Open source Data

Archives of Toxicology (2020) 94:2435–2461
https://doi.org/10.1007/s00204-020-02802-6

IN VITRO SYSTEMS

The EU-ToxRisk method documentation, data processing and chemical testing pipeline for the regulatory use of new approach methods

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essment, based on new approach methods (NAM), requires the use of batteries of assays, where individual tests

New Approach Methods in Safety Assessment
EU-ToxRisk Solutions

Who we are

The EU-ToxRisk Commercial Partnership is a joint venture between organisations providing coordinated integrated solutions to industrial problems in safety assessment. The partners bring experience and resources together to provide a one-stop shop in safety assessment solutions.

We jointly have experience in New Approach Methodology in safety assessment, predictive toxicology, *in vitro* screening, computational modelling, toxicogenomics, read across, tiered strategies, data science, product design, risk assessment and regulatory assessment.

Our Expert Team

- **Barry Hardy**, Edelweiss Connect GmbH, coordinator
- **Costanza Rovida**, CAAT-Europe
- **Bart van der Burg**, BDS
- **Bas ter Braak**, Leiden University
- **Monika Kijanska**, InSphero
- **Paul Jennings**, Vrije Universiteit Amsterdam
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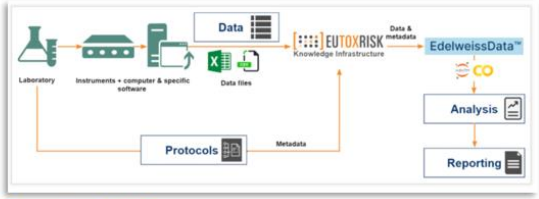
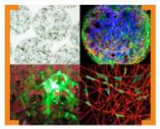


What we provide

Solutions to:

- Tiered strategies in safety assessment
- Evaluation of toxicological endpoints: e.g., liver, kidney, neurotoxicity, skin, eye, endocrine disruption
- Integrated screening and data analysis across multiple technologies
- High quality best practices in protocols, data generation and processing
- Data mining and modelling to supporting decision making and jobs to be done
- Product ingredient screening and evaluation
- Formulation testing and assessment



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Case studies

Industry driven cases studies (customer decides):

- Case study on parabens in collaboration with **Cosmetics Europe** (L'Oreal, P&G, Unilever, Clariant, etc.); EDC effects (EATS module) mitochondrial tox (EU-ToxRisk: UL,BDS,VU,DC)*.
- **Syngenta** case study on proprietary compounds with DART issues (EU-ToxRisk: UL,SimCyp, DC,TNO,UKN,VU,FHG,BDS)
- **Internal industry** driven case studies (Ab initio CS12/CS16)

* OECD Case Studies on Integrated Approaches for Testing and Assessment (IATA):

2019	1	Case Study on the use of an Integrated Approach to Testing and Assessment (IATA) and New Approach Methods to inform a Theoretical Read-Across for Dermal Exposure to Propylparaben from Cosmetics	Safety assessment workflow	Reproductive toxicity	Published

➢ **D12.4: Industry case studies BDS 12-2021**

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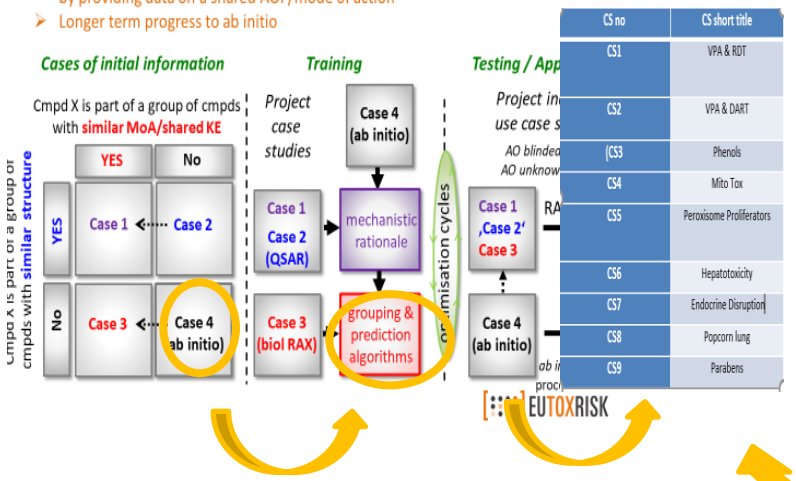
Application - Case Studies

1. Develop and test via case studies as drivers for application of approaches

- Integrate data from NAMs into regulatory risk assessment framework
- First step: Use NAMs to reduce the uncertainty of a read-across approach e.g. by providing data on a shared AOP/mode of action
- Longer term progress to ab initio



2. R.A.B. - feedback and refinement mechanism

EFSA, EPA, ECHA, SCCS, FDA, OECD, NTP, BfR

3. External feedback and engagement. Regulatory

ECHA, OECD, Japan NIH, HC, US EPA, NIH, EFSA

NAM-supported read-across: from case studies to regulatory guidance in safety assessment

21-22 May 2019, Hotel Korpilampi, Espoo, Finland

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READ Across Case studies

- Key strengths identified, also where additional guidance would be needed
- Encouraging to see that some of the comments highlighted how they could see the approaches being applied
- Case studies – how do we define similarity remains an open question especially from a NAM perspective
  - NAMs provide data to show that differences between target and source exist – is this increasing uncertainty or being explicit about expected differences.

- How to report and interpret new model data – eg Data quality and the applicability domain of in silico models in relation to uncertainties
- How to explain “new” computational approaches used for context to non experts & availability
- Differences in how to apply – running from
- could be used as part of WoE within existing regulatory context
- to prioritisation
- to currently not applicable

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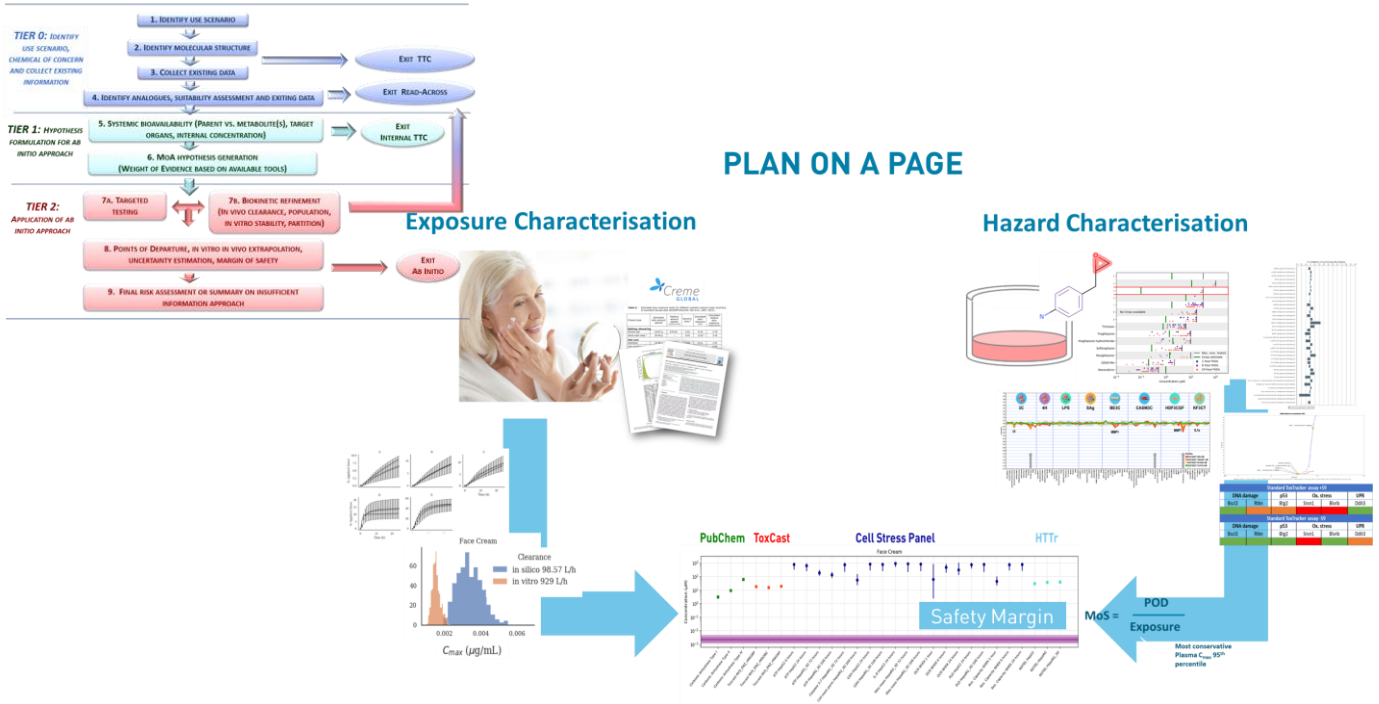
Drive for New Approaches –Exposure led NGRA

Team based



- 5 Teams to assess data and provide NAM use scenarios
- 10 case studies – subset of defined compound set -JRC
- No chronic repeat toxicity data available
- Identify and document key findings for future guidance document
- What worked well – what gaps were remaining
- Confidence in decision

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A Remaining Challenge – Training and Dissemination

"However, in order to accept the final results, it would be necessary to build a team of experts of PBPK, in vitro toxicology, toxicity mechanisms and in vivo toxicology and experts who can interpret them in an integrated manner. "

- 2 summer schools + winter school
- 4 workshops
- 10 webinars

Need to shift focus from BAU to enable training to understand new technologies contexts and key questions that arise from them. Therefore, enabling multi-disciplinary teams to be built that can engage with future submissions.

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Conclusions

- EU-ToxRisk has moved the needle in its vision to shift the paradigm and progressed the case for uptake of NAMs in both priority setting and risk assessment. Helping to meet the challenges of the new Chemical Sustainability strategy
  - Driven new scientific developments filling gaps in current capability
  - The focus on bringing key stakeholders, regulators, industry and scientists together in a neutral and creative scientific environment has been a significant achievement and fills a necessary gap
  - Facilitated by case studies to examine stakeholder needs
- However in order to maximise the return on investment in projects such as EU-ToxRisk
  - Need for increased regulatory participation to increase acceptance and uptake of these tools as alternatives to in vivo options where they can be targeted currently and put into action today
  - Incentivise the requirement for investment in training in new technologies for regulators and how to pull in specialist knowledge

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Thank you