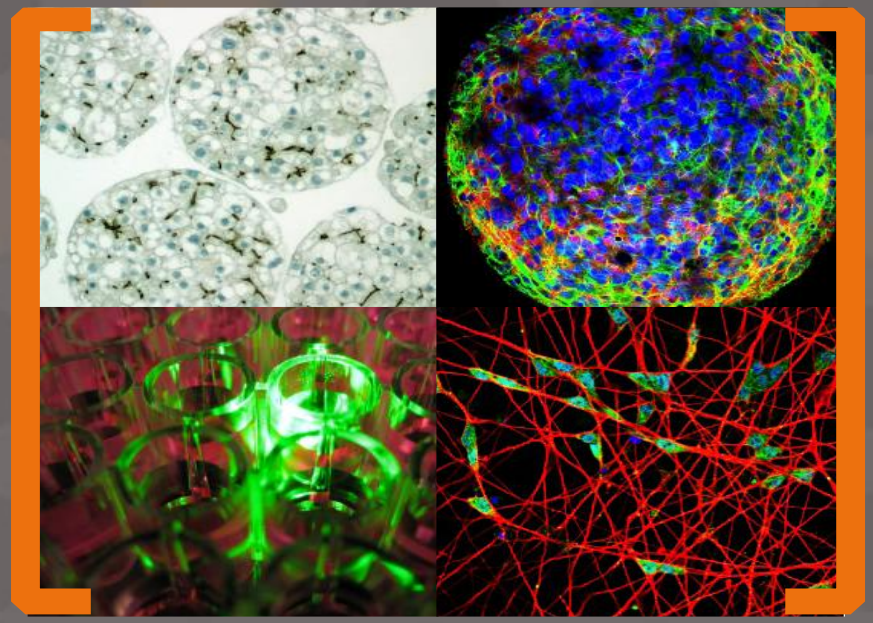
EU-ToxRisk RAx advisory Document



Hennicke Kamp
BASF Metabolome Solutions GmbH, Germany

04.11.2021

EU-ToxRisk's objective: apply NAMs in hazard & risk assessment

First panel of EU-ToxRisk case studies focused on
how to apply NAM in a read across assessment context

→ ***Target to develop guidance on the use of NAM data for read-across***

Four advanced **case studies** were submitted for **stakeholder consultation** and review to:

- ❑ RAB (Regulatory Advisory Board) EU-ToxRisk (Jan 2019)
- ❑ Expert Workshop Espoo (May 2019)
- ❑ **OECD IATA Case Study Project** **(April 2019)**

Meeting Report

NAM-Supported Read-Across: From Case Studies to Regulatory Guidance in Safety Assessment

doi:10.14573/altex.2010062 Rovida et al., 2021

Impact: **refinement** and **restructuring** of the '**Advisory Document** on NAM-enhanced read-across' (provisional title)

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The ‘Advisory Document on NAM-enhanced read-across’

The Purpose of the advisory document

The ‘Advisory Document on NAM-enhanced read-across’

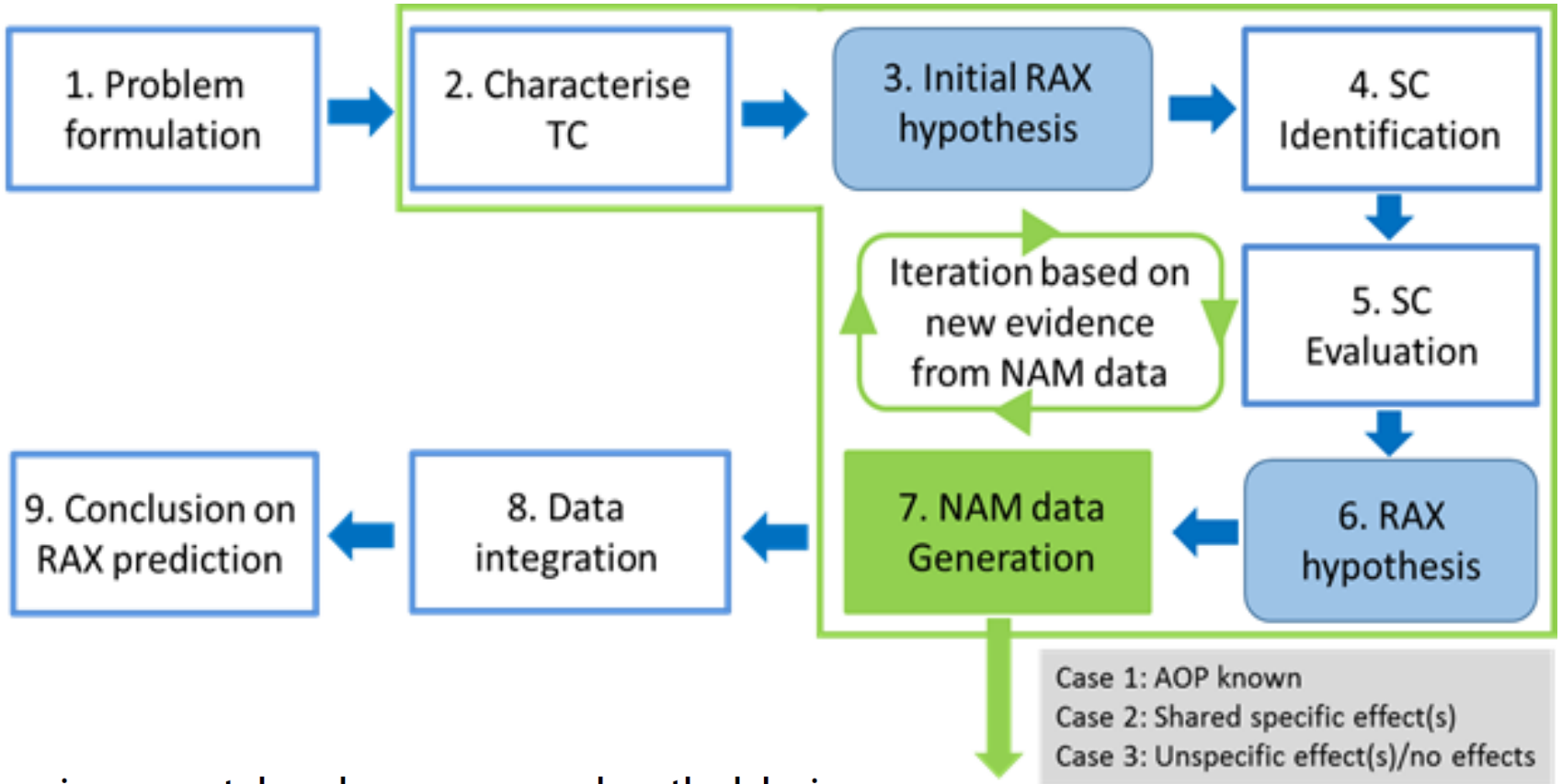
The Purpose of the advisory document

- recommendations for the use of **new approach methodologies** (NAMs) in read-across
- substantiate a **read-across hypothesis** on the level of toxicokinetic/-dynamic properties

- different **application scenarios** (e.g., decision making in relation to screening, prioritization, regulatory data gap filling)
- different **application areas** (e.g., industrial chemicals, agrochemical, cosmetics, food)
  The intended application defines the acceptable uncertainty of the read-across extrapolation and impacts the data generation strategy.

- guidance on **reporting** a NAM-based read-across case and the methodologies used to generate and assess the data
- Structured along the **read-across workflow**

The Read-Across Workflow – the read across steps



Escher et al., 2019

Towards grouping concepts based on new approach methodologies in chemical hazard assessment: the read-across approach of the EU-ToxRisk project

Sylvia E. Escher[1] · Hennicke Kamp[2] · Susanne H. Bennekou[3] · Annette Bitsch[1] · Ciarán Fisher[4] · Rabea Graepel[5] · Jan G. Hengstler[6] · Matthias Herzler[7] · Derek Knight[8] · Marcel Leist[9] · Ulf Norinder[10] · Gladys Ouédraogo[11] · Manuel Pastor[12] · Sharon Stuard[13] · Andrew White[14] · Barbara Zdrazil[15] · Bob van de Water[5] · Dinant Kroese[16]

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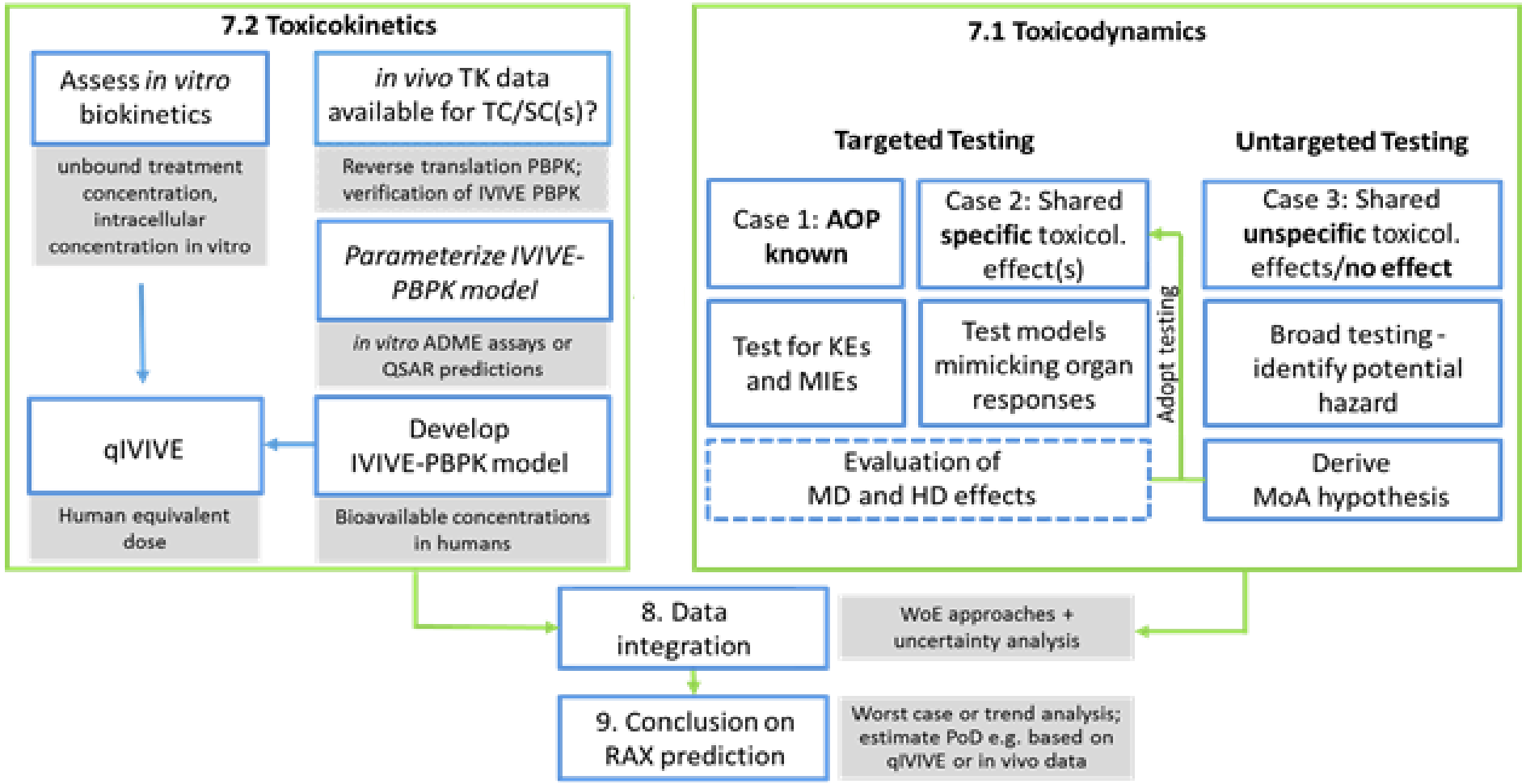
The Read-Across Workflow – Learnings from the case studies

Source compound (SC) identification & evaluation (Step 4 & 5)

- clearly documented and reproducible process
- SC selection based on structural, biological and/or PC properties
- clear justification along the identified analogues and why some might be discarded…
  - Compile and document all existing in vivo, in vitro and in silico data
  - Evaluate (dis)similarities within the source compounds
  - Screen for structural alerts or QSAR models to identify MIEs
- **supportive NAM testing to confirm RAX hypothesis and suitability of the selected source compounds or to rule out conflicting data**

"Selection bias is one of the most serious „crimes" in RAX!"

The Read-Across Workflow – the read across steps



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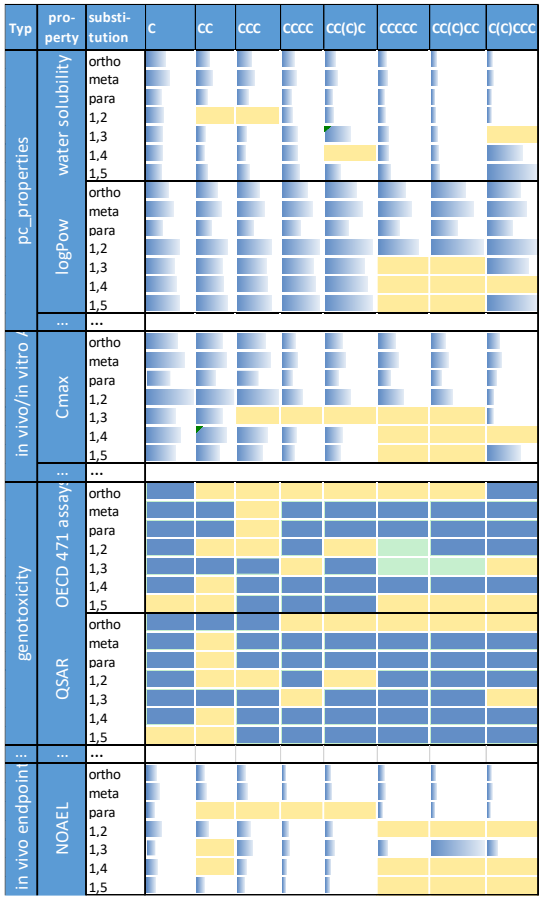
The Read-Across Workflow – Learnings from the case studies

Data analysis and uncertainty assessment (Step 8)

- Evaluate individual data streams for **quality**
- Consider **homogeneity/ heterogeneity** in the data set
- application of **inclusion and exclusion criteria:** scientific justification & transparent documentation for omission of data
- Generation of data matrix; assessment of **concordance of data** across compounds; application of cluster/ trend analyses
- Identify, quantitate and **assess** sources of **uncertainty**
- **Further development needed!**



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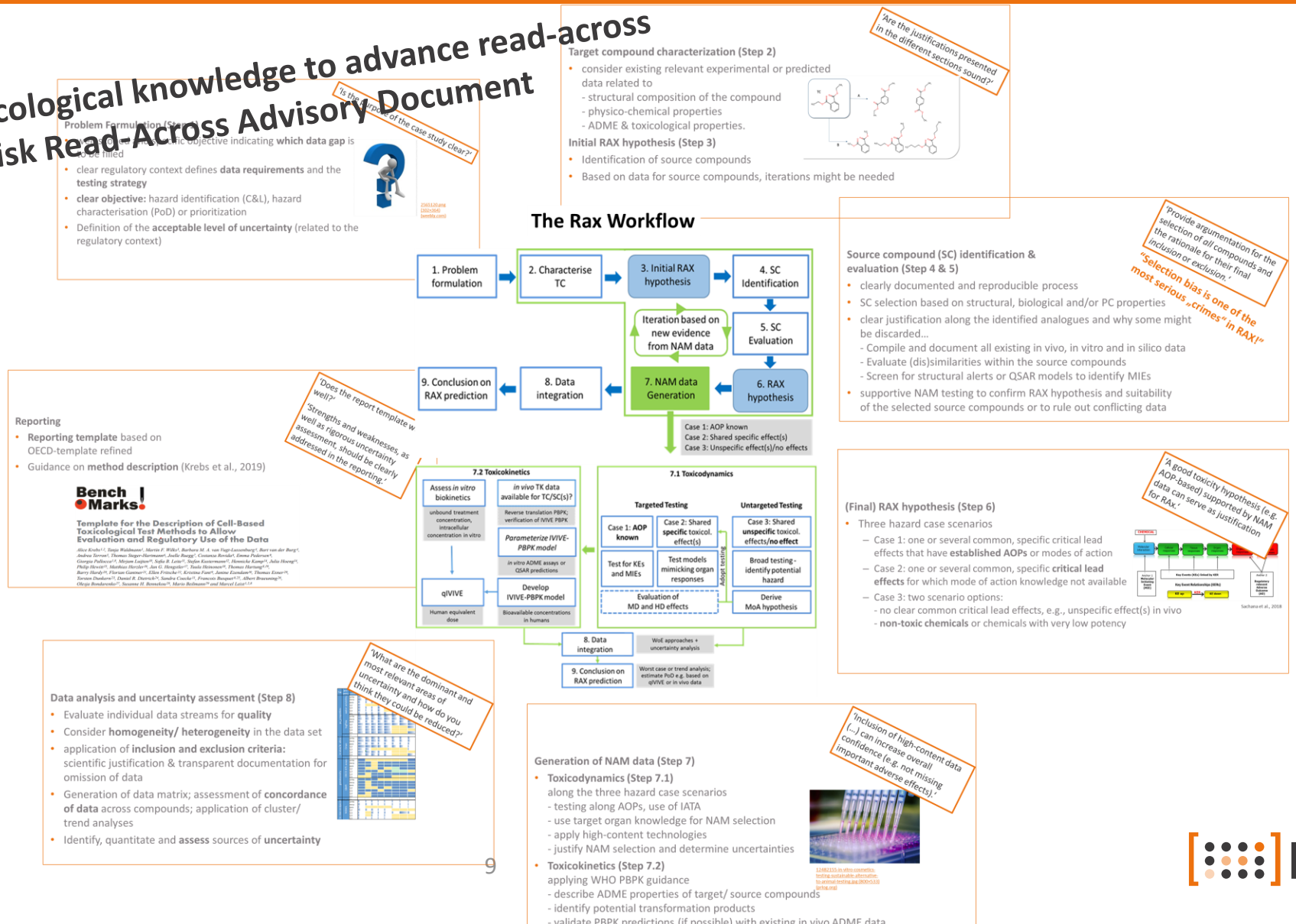
The Read-Across Workflow – Learnings!

Poster:
Impact #2: Improved toxicological knowledge to advance read-across procedures: The EU-ToxRisk Read-Across Advisory Document



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The ‘Advisory Document on NAM-enhanced read-across’

One main learning: Documentation & Reporting!

- “Ideally, NAM-data for regulatory purposes should be generated under GLP/ GLP-like…” *(Stakeholder Discussion Oct 2021)*
- **Reliability (Fitness-for-purpose) of methods to be documented** (Krebs et al., 2019)

Template for the Description of Cell-Based Toxicological Test Methods to Allow Evaluation and Regulatory Use of the Data

Alice Krebs[1,2], Tanja Waldmann[1], Martin F. Wilks[3], Barbara M. A. van Vugt-Lussenburg[4], Bart van der Burg[4], Andrea Terron[5], Thomas Steger-Hartmann[6], Joelle Ruegg[7], Costanza Rovida[8], Emma Pedersen[9], Giorgia Pallocca[1,8], Mirjam Luijten[10], Sofia B. Leite[11], Stefan Kustermann[12], Hennicke Kamp[14], Julia Hoeng[14], Philip Hewitt[15], Matthias Herzler[16], Jan G. Hengstler[17], Tuula Heinonen[18], Thomas Hartung[8,19], Barry Hardy[20], Florian Gantner[21], Ellen Fritsche[22], Kristina Fant[9], Janine Ezendam[10], Thomas Exner[20], Torsten Dunkern[23], Daniel R. Dietrich[24], Sandra Coecke[11], Francois Busquet[8,25], Albert Braeuning[26], Olesja Bondarenko[27], Susanne H. Bennekou[28], Mario Beilmann[29] and Marcel Leist[1,2,8]

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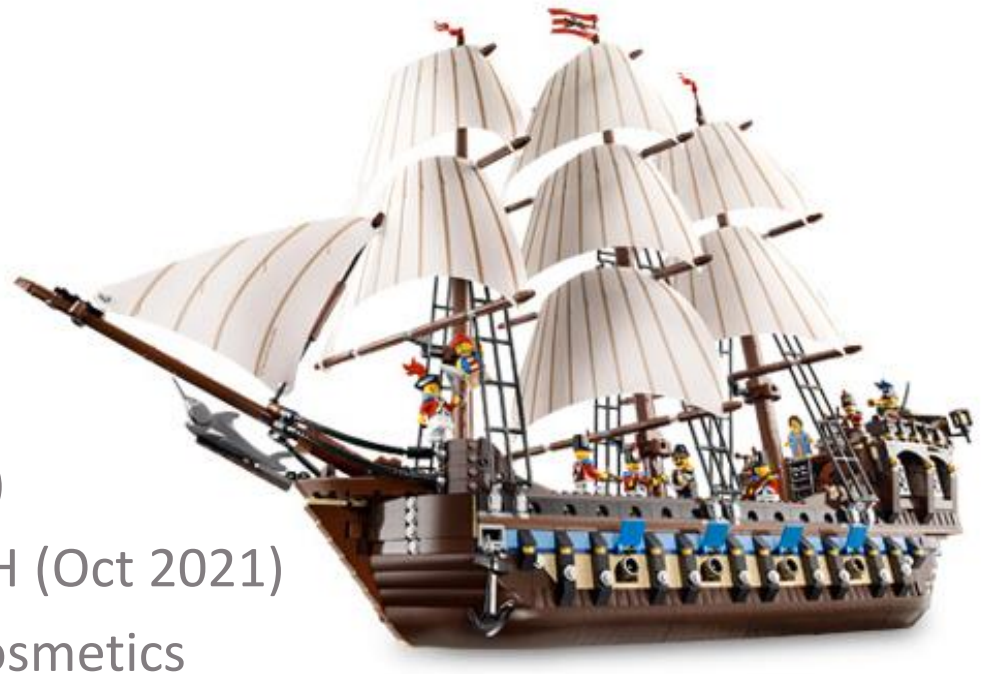
The ‘Advisory Doc on NAM-enhanced read-across’ - Summary

Status Quo of the advisory document

- **Comprises learnings of EU-ToxRisk**
- EU-ToxRisk achievements currently presented to / discussed with
  - EFSA WG on Grouping and Read-Across (Sep 2021)
  - Regulatory and Industry Stakeholders under REACH (Oct 2021)
  - Regulatory and Industry Stakeholders under the cosmetics Directive (Dec 2021)
- Translation into “living document” needed → OECD? EFSA?
- **Further work necessary: P**eople, **P**rojects, **P**ots *(of money)*



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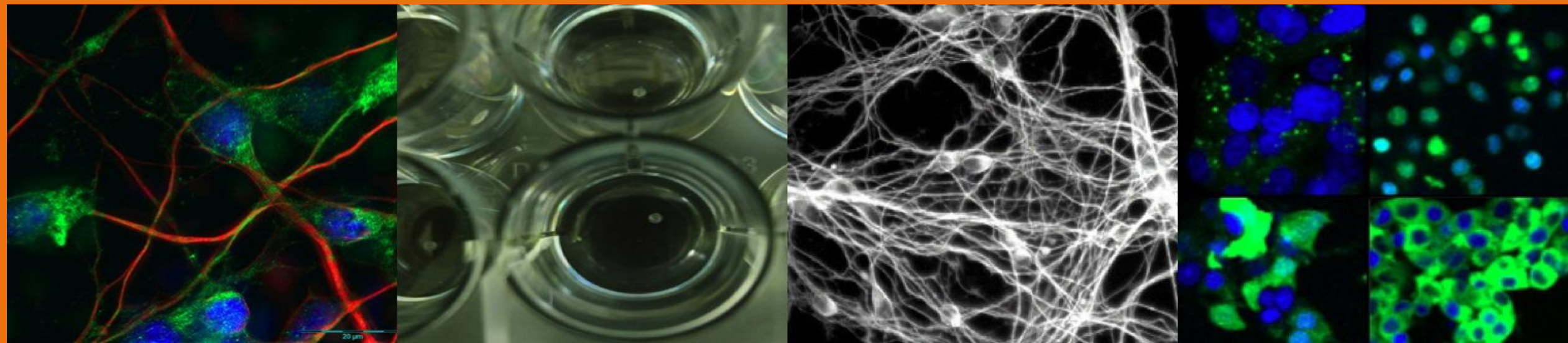
Thank you for your attention!



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Problem Formulation (Step 1)

- well-scoped and specific objective indicating **which data gap** is to be filled
- clear regulatory context defines **data requirements** and the **testing strategy**
- **clear objective:** hazard identification (C&L), hazard characterisation (PoD) or prioritization
- Definition of the **acceptable level of uncertainty** (related to the regulatory context)

2565120.png (302×364) (weebly.com)

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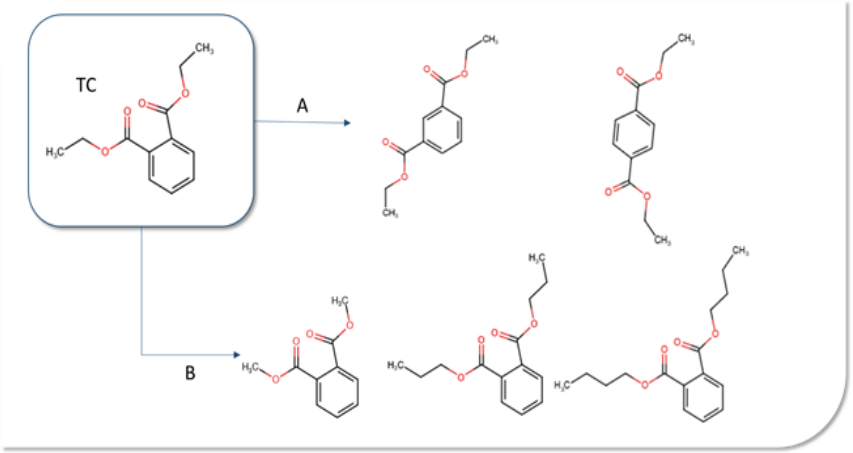
Target compound characterization (Step 2)

- consider existing relevant experimental or predicted data related to
  - structural & physico-chemical properties
  - ADME & toxicological properties.



Initial RAX hypothesis (Step 3)

- Identification of source compounds
- Based on data for source compounds, iterations might be needed

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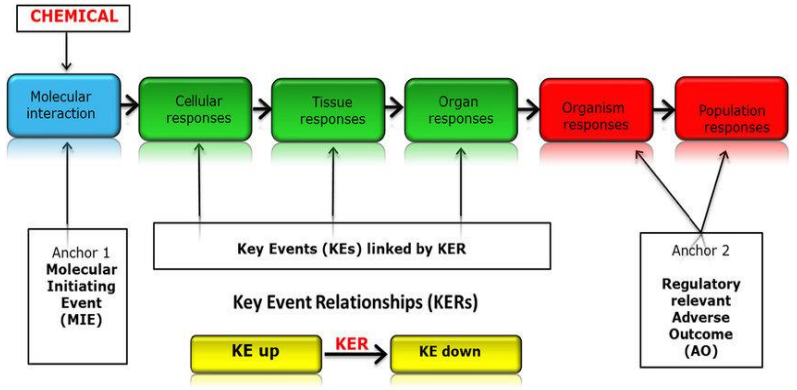
(Final) RAX hypothesis (Step 6)

- Three hazard case scenarios
  - Case 1: one or several common, specific critical lead effects that have **established AOPs** or modes of action
  - Case 2: one or several common, specific **critical lead effects** for which mode of action knowledge not available
  - Case 3: two scenario options:
    - no clear common critical lead effects, e.g., unspecific effect(s) in vivo
    - **non-toxic chemicals** or chemicals with very low potency



Sachana et al., 2018

‘A good toxicity hypothesis (e.g. AOP-based) supported by NAM data can serve as justification for RAx.‘

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Generation of NAM data (Step 7)

- **Toxicodynamics (Step 7.1)**
  along the three hazard case scenarios
  - testing along AOPs, use of IATA
  - use target organ knowledge for NAM selection
  - apply high-content technologies
  - justify NAM selection and determine uncertainties
- **Toxicokinetics (Step 7.2)**
  applying WHO PBPK guidance
  - describe ADME properties of target/ source compounds
  - identify potential transformation products
  - validate PBPK predictions (if possible) with existing in vivo ADME data

12482155-in-vitro-cosmetics-testing-sustainable-alternative-to-animal-testing.jpg (800×533) (prlog.org)