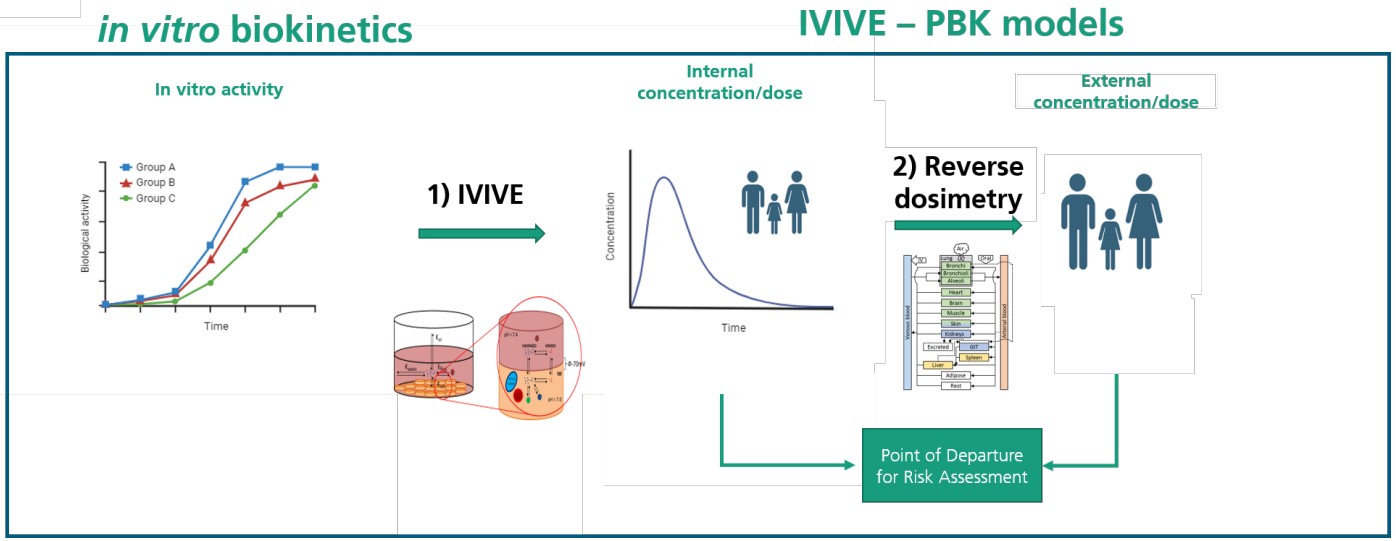
Which assessment areas should be prioritised for early implementation in pesticides and biocides, considering scientific readiness, regulatory need and the potential reduction in animal use?

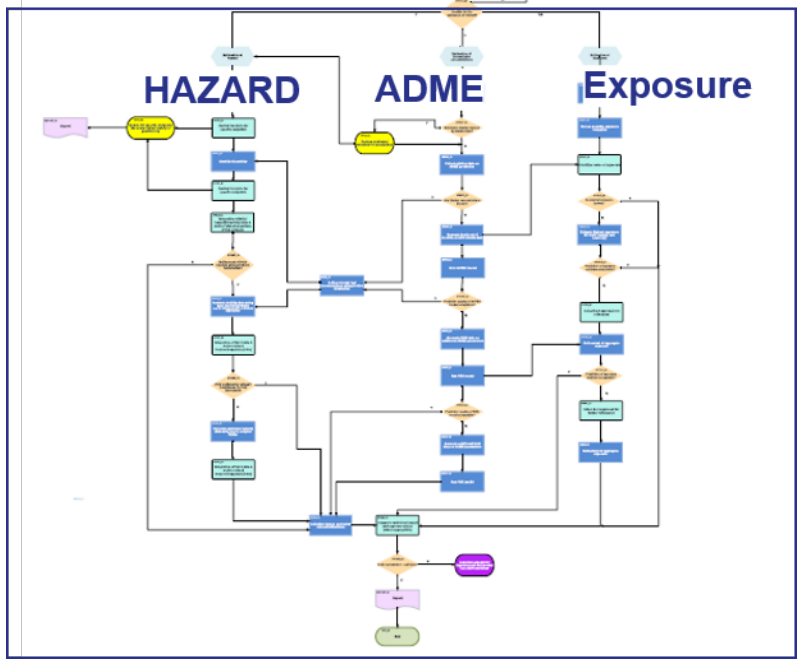
Dr. Sylvia Escher, Division Director Safety Assessment and Toxicology, Head of Department In Silico Toxicology, Fraunhofer ITEM, Hannover, Germany

Next Generation Risk Assessment (NGRA) in a Nutshell

Regulatory standard test requirements pesticides

- Assessment of Systemic Toxicity – e.g. 90d studies
- ADME studies

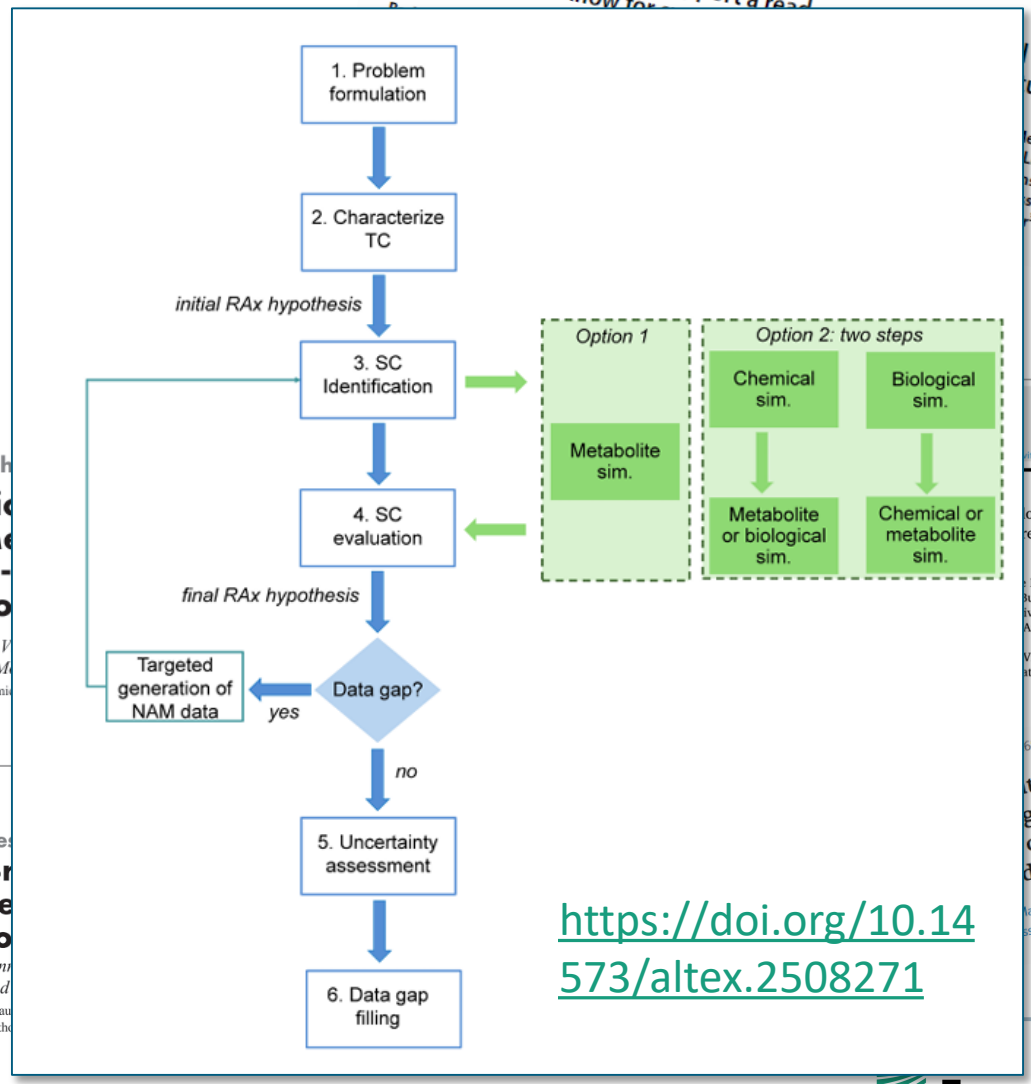




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Integrate NAMs into Read-Across Approaches to predict the Toxicological properties of data poor compounds

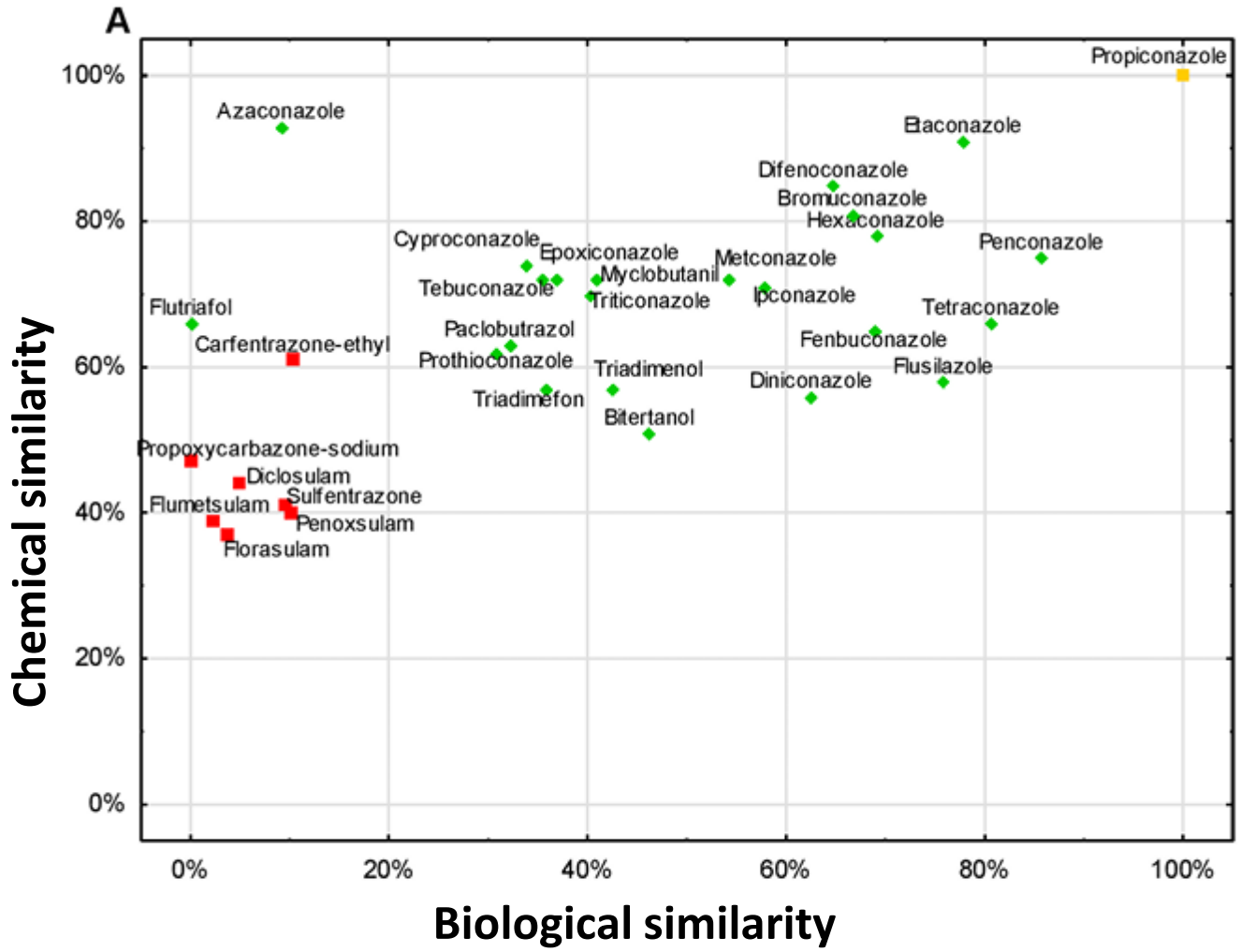
- Use **metabolite similarity** (e.g. in silico predicted) for the selection of source compounds (SCs, EFSA RAX project)
- **HT-NAMs („omics“, reporter assays)** to support biological similarity - SC assessment (EUTOXRISK/RiskHunt3R)
- **Bottom-up PBK models** for i) in vitro to in vivo extrapolation, ii) demonstrate shared kinetic properties - SC assessment (EUTOXRISK/RiskHunt3R/ZeroPM/PARC/EFSA ADME4NGRA)
- Follow up HT-testing by **targeted NAM testing based on read-across hyothesis**, increase PoD_{NAM} (EUTOXRISK/RiskHunt3R)



https://doi.org/10.14573/altex.2508271

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Chemical Plus Biological Similarity - Example Pesticides (Propiconazole)

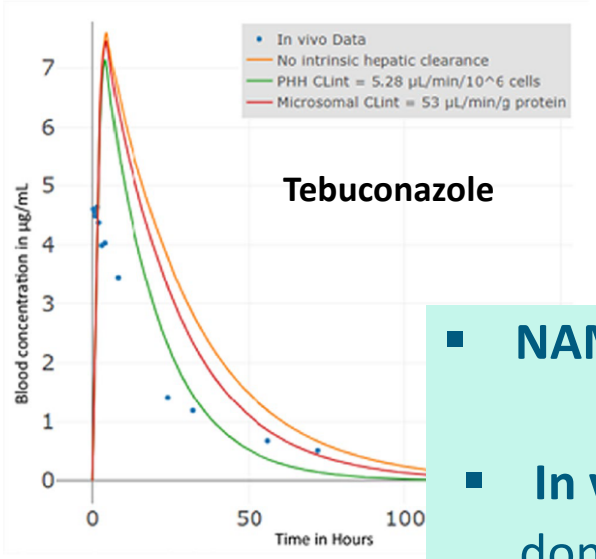


All available data

Biological data discriminate better based on read-across hypothesis e.g. critical adverse effect and known AOP

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Kinetic Assessment - PBK modelling /in vitro biokinetics



- Within read-across the quantification of uncertainty is possible by comparing predicted to measured data for one/few data rich compounds.

Beyond read-across

- **NAMs in read-across** cases and **kinetic modelling** have demonstrated their predictivity and performance – **fit for purpose**.
- **In vitro assay standardisation** e.g. for ADME parameter needs to be done. E.g. define bench mark compounds to account for variability of primary cells (OECD initiative ongoing)

lels are applicable

factor of 10.

nservative site

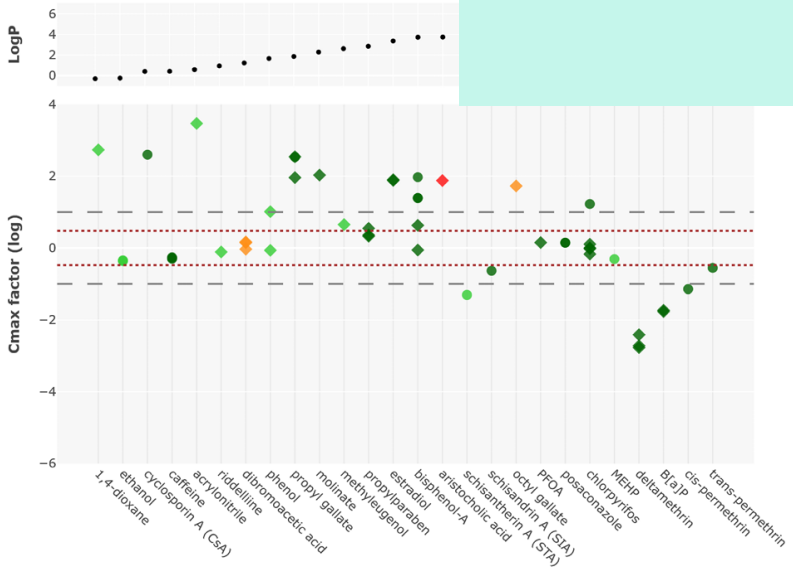


Table 2 Overview of model's performance on each chemical for C_{max}, T_{max} and AUC Results are presented as the total average of all studies for their respective chemical.

Factor to in vivo study	<3	3—10	>10
C_{max}	8 (31%)	5 (19%)	13 (50%)
T_{max}	12 (46%)	8 (31%)	6 (23%)
AUC	8 (31%)	5 (19%)	13 (50%)

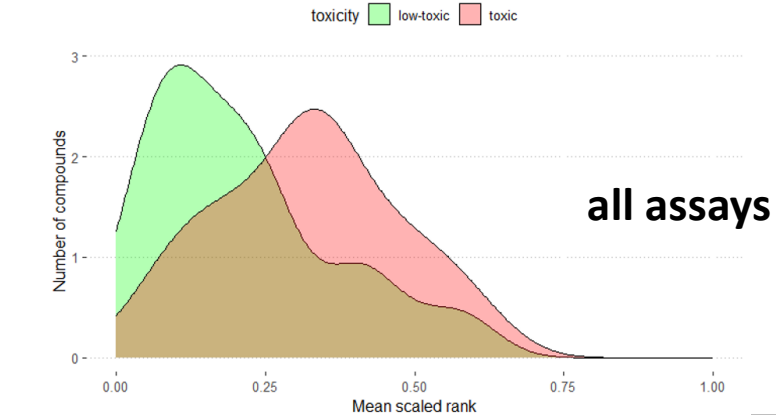
https://doi.org/10.1007/s00204-025-04268-w
https://doi.org/10.1007/s00204-026-04443-7

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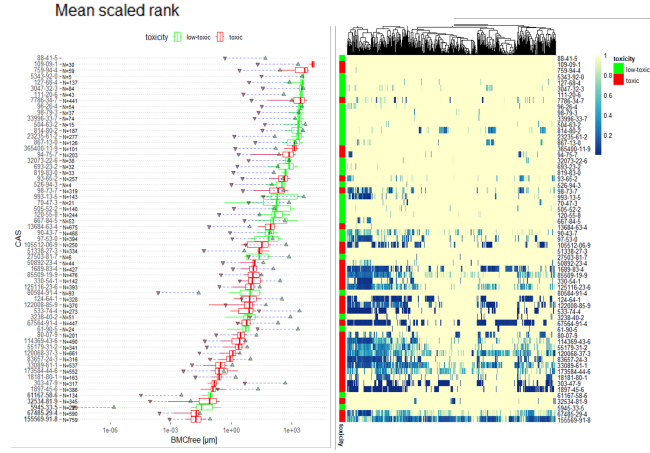
Challenges and Current Implementation Barriers

- Without ankering in vivo data - the definition of a „**good enough in vitro testing battery for hazard identification**“ is a challenge
- First case studies on systemically toxic compounds demonstrate that **HT-NAMs discriminate Toxic from Low Toxic Compounds (STOT_RE)**
- **HT-assay overpredict toxicity** when used to derive PoD_{NAMs}
- Too many options - no consensus on how to derive a **POD_{NAM}**

- Joint case studies needed to define the **criteria for the use of more complex assays**
- Oral route is not the only one – more evidence needed for **inhalation exposure**



Cell painting



PoD NAM

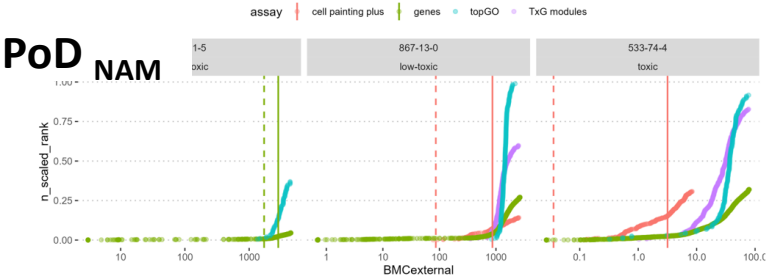


Figure 7: Analysis for PODs using Ortho tertiary butyl cyclohexanyl acetate (CAS 88-41-5), Triethyl phosphonoacetate (CAS 867-13-0) and Dazomet (CAS 533-74-4) as examples. Solid vertical lines indicate the minimum median assay BMC of the respective compound, dashed lines indicate the Median Absolute Deviation (MAD) subtracted from the median.

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