Proposals for short-midterm solutions to increase use of NAMs under current system

New approach methodologies workshop: Towards an animal free regulatory system for industrial chemicals

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- → Key elements of the current system
- → Proposed way forward
- → Conclusions

The starting point

While considering a system based on non-animal test methods, main elements of the horizontal system should be maintained:

- Defined **hazard classes** based on clear criteria
  - ✓ worldwide harmonisation via GHS
  - ✓ with associated generic risk management measures (EU)
- **Standard information requirements** allowing conclusive outcome for:
  - ✓ classification & labelling (C&L)
  - ✓ reference doses for risk assessment
- **Quality data** for decision making:
  - ✓ reliable comparable and re-usable
  - ✓ allowing mutual acceptance of data

→ **Currently we don't have NAM solutions ready that cover these 3 main elements!**

Proposed way forward

Proposed way forward in three steps:

Identify critical needs for transit to animal free system to steer NAM development

Step 1. Define

Apply already available NAMs under current system

Step 2. Demonstrate

Re-think overall system to enable NAMs & **Redefine** main elements of horizontal approach

Step 3. Re-design

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Step 1: identify (and address) critical needs

Demonstrate NAMs can derive protection levels comparable with current ones

- **Hazard identification:** Ability to demonstrate that NAMs, (e.g. an integrated *in vitro/in silico* system) can be used to allow a conclusive outcome on the (lack of) hazardous properties for a given regulatory endpoint
- **Hazard characterisation:** Ability to reliably identify hazard based on changes at the molecular/cellular level instead of observed adversity in an organism
- **Extrapolation:** Ability to reliably convert nominal concentrations measured or predicted by NAMs into external doses used to set safety levels, to communicate the hazard and assess the risks

Step 2: Apply NAMs under current system

There is significant potential for **refinement** and **reduction**, using tools already available in the following areas:

For lower tier endpoints

- **Developments of *in silico* methods (e.g. QSARs)** with higher predictive capacity and broader applicability domain for hazard and risk assessment

For higher tier endpoints

- Inclusion of **'omics enhanced *in-vivo* studies** to generate molecular data in an entire biological system
- Better utilisation of NAMs to support **read-across and grouping**

Step 3: Adapt overall system (if necessary)

While closing critical gaps identified in step 1 and gaining confidence in step 2, we can start considering what is needed for a new framework. Potential areas for consideration are:

- How to derive reference values for risk assessment from molecular data (not adverse effects)
- How to calibrate the system against expected and well-defined protection goals
- Revision or development of C&L criteria which are suitable for NAMs
- Throughput/performance and cost optimisation

Applying NAMs under current system

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Reliable *in silico* methods

Scientific validity of the **model** is important, however clear criteria for reliability and relevance of the **prediction** are of key importance for wider regulatory acceptance.

OECD project on developing QSAR Assessment Framework

→ Revised criteria for the assessment of (Q)SAR models

→ Newly introduced criteria for the assessment of (Q)SAR results

- ✓ Correct input to the model
- ✓ Substance within applicability domain
- ✓ Reliable prediction
- ✓ Outcome's fit for purpose

Why 'omics enhanced *in vivo* studies

→ Necessary for further development of NAM methodology for hazard/risk assessment

→ Significant potential for refinement, reduction while transiting to replacement

→ Way to deal with 'difficult to test' substances in the future

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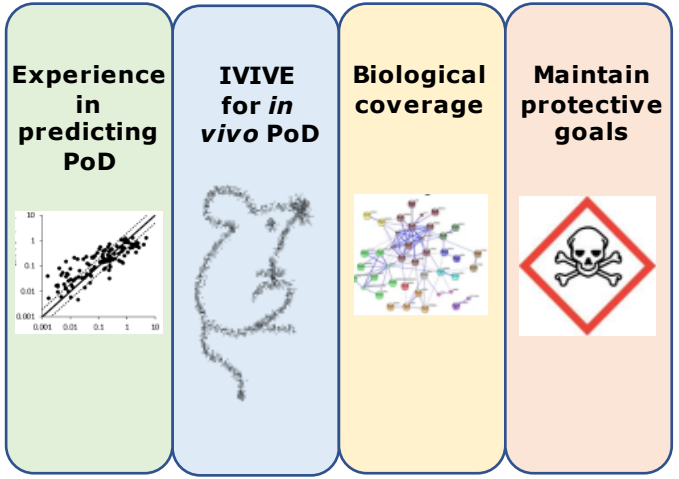
Development of NAM methodology for hazard/risk assessment

Currently we struggle with too many questions…

To address systemic toxicity the following elements needs to be addressed:

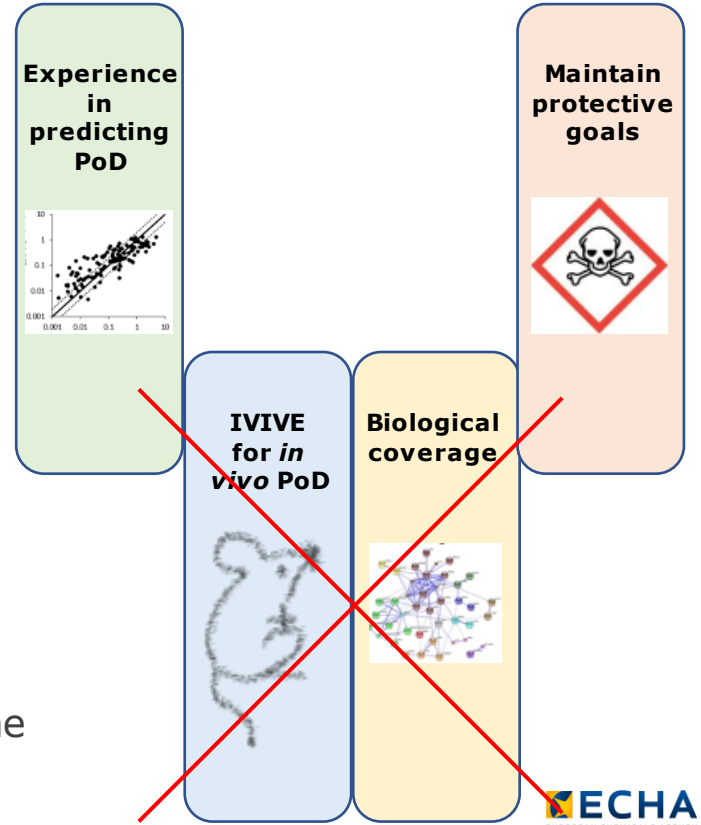
- Demonstration that vast simplification in the **biological system** will not lead to significant **protection gaps**
- **Derivation of reference values** from molecular data (and not observed adversities)
- Reliable ***in vitro* to *in vivo* extrapolation** (IVIVe) working for majority of industrial chemicals
- Calibration of the new system to maintain **protective goals comparable** with classical toxicity studies



An *in vivo* system can help to eliminate some of the unknowns from the equation!

Application of *in vivo* 'omics is a pragmatic approach to reduce problem complexity

- → 'omics approaches can generate molecular data in an entire biological system
  - ✓ Inform on multi-level cellular disturbances
  - ✓ Allow system-wide approach to address biological complexity
- → When combined with in vivo testing, 'omics approaches allow
  - ✓ Comparison with classical toxicity studies (maintain protective goals)
  - ✓ Confidence in derivation of reference values
- → No need for IVIVe
  - ✓ when toxicodynamic responses are combined with toxicokinetics, in vivo data can help refine IVIVe models for industrial chemicals



Potential for 3Rs

3 Rs:

→ Refine

- ✓ Shorter test duration
- ✓ Reduced pain and stress
- ✓ More objective way to derive reference values
- ✓ Potential for mechanistic insights + info on human relevance

→ Reduce

- ✓ Individual samples (re-)used for multiple purposes
- ✓ Reduced demand for multiple tox studies
- ✓ Potential for grouping and read-across

→ Replace

- ✓ Support the development of methodology critical for non animal testing
- ✓ Allows to build experience and confidence on NAMs during the journey

Dealing with difficult substances

Current experience shows that not every substance can be tested/predicted using *in vitro/in silico* systems

How to deal with these limitations in the future system which will be based on animal free NAMs?

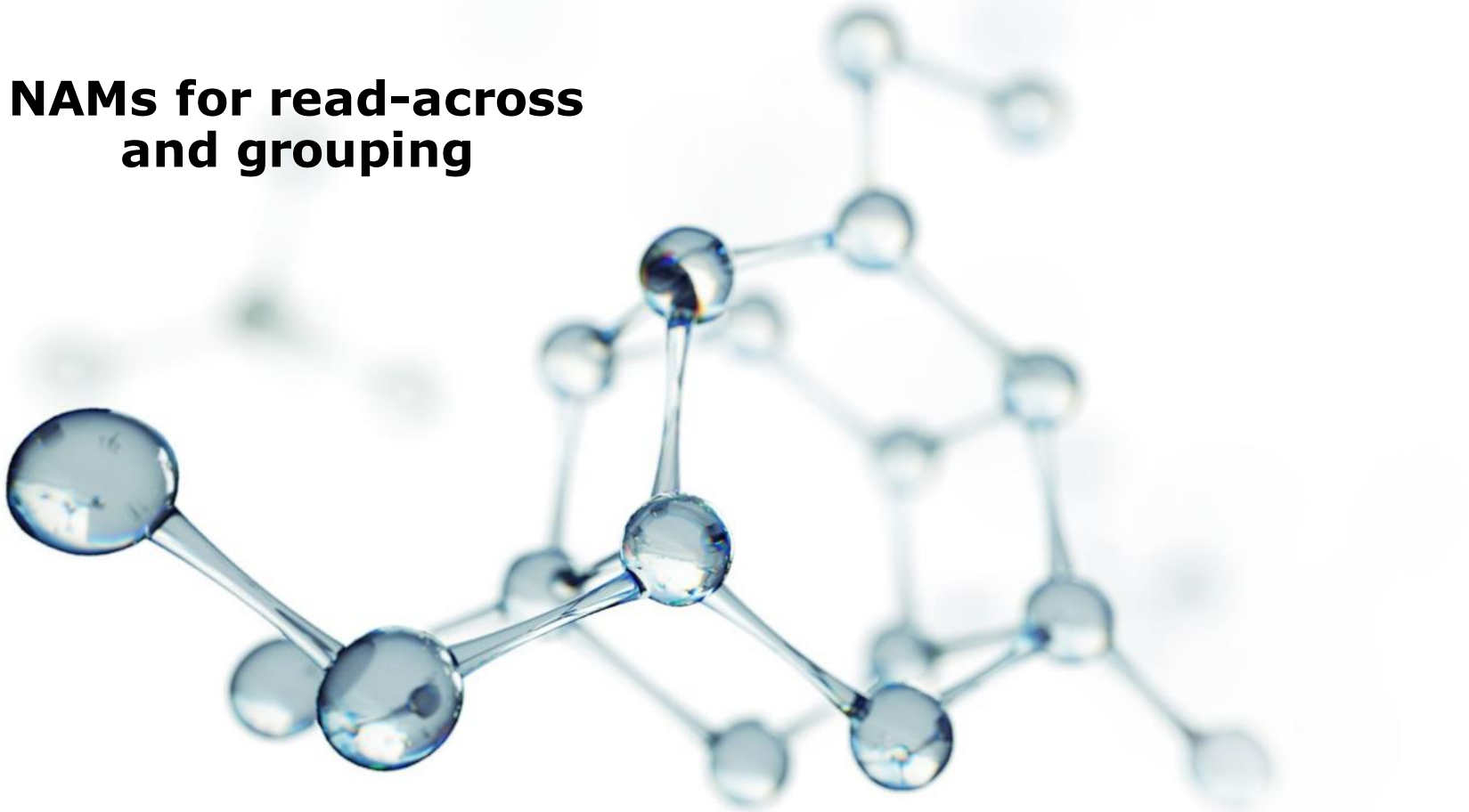
→ Maintaining classical tox studies to deal with exceptions?

- ✗ Not effective
- ✗ Introduces inconsistency in how hazard/risk is identified
- ✗ Capacity to run classical tox studies will decrease with time

→ Use of 'omics enhanced and optimised in vivo assays

- ✓ Design can be further optimised
- ✓ NAMs parameters are used to identify and characterise hazard/risk
- ✓ Wide access to NAM based testing
- ✓ Human relevance can be addressed by growing knowledge of pathway conservation between the species

NAMs for read-across and grouping



Are NAMs suitable for supporting grouping and read-across?
Possibly, but for successful application, additional criteria need to be developed…

→ Toxicological significance of the model used to generate NAM data
- Is the model capable of expressing relevant toxicity?

→ What is similar and what not
- What level of similarity in molecular response should be considered to justify toxicological similarity?

→ Interpretation of molecular data to substantiate the grouping hypothesis
- How feasible is the interpretation of the NAM data to substantiate a grouping hypothesis, considering specific endpoint that is being read across?

Conclusions

- → There is a need to agree on critical elements to be addressed for transition into an animal free system
- → Joint and focussed efforts are needed to fill the gaps
- → In the meantime, NAMs can be utilised to refine, reduce and replace animal testing under the current system
- → Developing, agreeing and sharing criteria for NAMs in regulatory applications is key for a wider acceptance

Thank you

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