Developing and applying new approach methods for regulatory applications

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Disclaimer: *The opinions expressed here are those of the author and do not necessarily reflect the views or the official position of the European Chemicals Agency.*

Overview

- → Our approach towards 3Rs
- → New Approach Methods (NAMs): A regulatory perspective
- → challenges …
- → … and opportunities
- → Regulatory acceptance
- → Outlook

Our approach towards 3Rs

(**R**eplacement **R**eduction **R**efinement)

Main pillars:

→ **Effective implementation of our integrated regulatory strategy**
Use of new approach methods (NAMs) for priority setting, addressing chemicals in groups, development of testing strategies based on read-across, forced data sharing at registration

→ **Investment in international activities that promote alternatives**
OECD QSAR Toolbox, support research flagship projects (EU-ToxRisk[1], ASPIS[2], PARC[3]) and active contribution to APCRA[4]

→ **Making data available**
Publishing information – key for developing new alternatives

1. An Integrated European 'Flagship' Programme: Driving Mechanism-based Toxicity Testing and Risk Assessment for the 21st century
2. Animal-free Safety assessment of chemicals: Project cluster for Implementation of novel Strategies
3. European Partnership for the Assessment of Risks from Chemicals (PARC)
4. Accelerating the Pace of Chemical Risk Assessment

New Approach Methods (NAMs)
A regulatory perspective

- → Balancing act – level of protection vs reducing animal testing
- → "Legal certainty" – a generic system like REACH requires "simple" decision points
  - to enable registrants to make informed choices for fulfilling legal obligations
  - to provide data needed in other legislation (e.g. Classification, Labelling and Packaging Regulation)
- → Time needed for developing alternatives vs ambition of regulating chemicals "now"

New Approach Methods (NAMs)
A regulatory perspective

→ Accepting different uncertainties
- we need to learn how to deal with uncertainties which are different from these in traditional in vivo tests
- some of the current NAMs are over conservative

→ New approach methods as standard information requirements:
- Lack of internationally recognised methods (Mutual Acceptance of Data - MAD)
- Showing added value for the current system not straightforward

Challenges ….

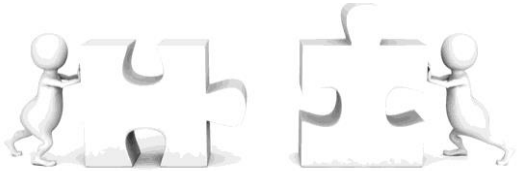
→ Replacing animal testing “one to one” successful for “simple” endpoints

- Support through OECD work on defined approaches
- Takes time to develop robust and reliable predictions

→ Replacing animal testing “one to one” not possible for complex endpoints under current regulatory framework

- REACH information requirements refer to animal tests
- The current system is regulated based on observed adversities
- Alternatives currently possible but assuming full equivalence to animal test
- Most new approach methods cannot predict adverse outcome at systemic level
- For many regulatory endpoints, the biology is not sufficiently understood to develop adverse outcome pathway (AOP)

… and Opportunities



- → Better integration of new approach methods in the current regulatory system
  - Use of NAMs for supporting read-across
  - ADME/Toxicokinetics
- → Better use of data – REACH, international data exchange, pharmaceuticals, agrochemicals – to support developments
  - Benchmarking
  - Work with case studies to redefine principles of risk assessment
- → Increase collaboration between regulators, researchers and industry
  - Support developing new approach methods suitable for regulatory needs - opportunities via APCRA, PARC, ASPIS, EPAA to:
    - demonstrate that NAMs can also work to confirm safety,
    - reduce level of conservatism in many current NAMs (better IVIVe?) and
    - derive "meaningful" reference values for regulatory risk assessment.

New approach methods - regulatory acceptance

Relevance

Using information from NAMs in regulatory decision-making

In comparison to current regulatory methods (guideline studies)

Reliability

Characterising performance and limitations of new methods

Consistency

Consolidating knowledge (e.g. mechanistic) and standardising tools to generate data

Harmonising handling and reporting of NAM data

Coverage

Assessing suitability for industrial chemicals

Defining domains of applicability

Confidence

Scientific acceptance/validation

Legal certainty

Ultimate goal: fully replace animal testing

→ Same level of protection or higher

→ Redefine main elements of current system

- Adversity, dose-response relationship, limit value derivation
- Predictive toxicology – e.g. regulate based on mode of action as an indicator of adversity?

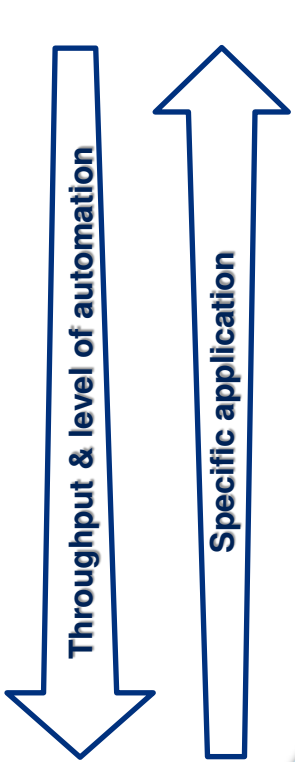
→ Possible changes in regulatory frameworks?

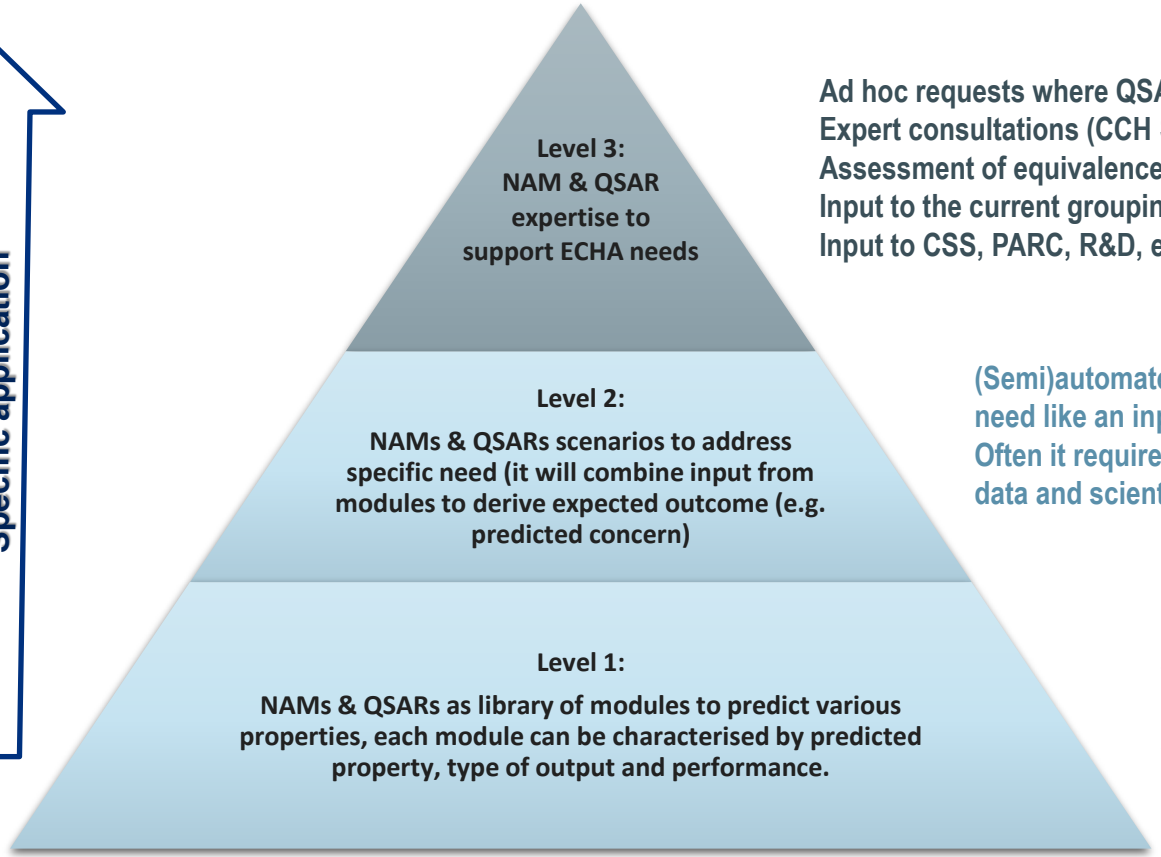
- REACH, CLP, GHS

→ Requires buy-in by all stakeholders, including the public

NAMs input to ECHA processes

NAMs (including QSARs) input to ECHA processes at 3 levels



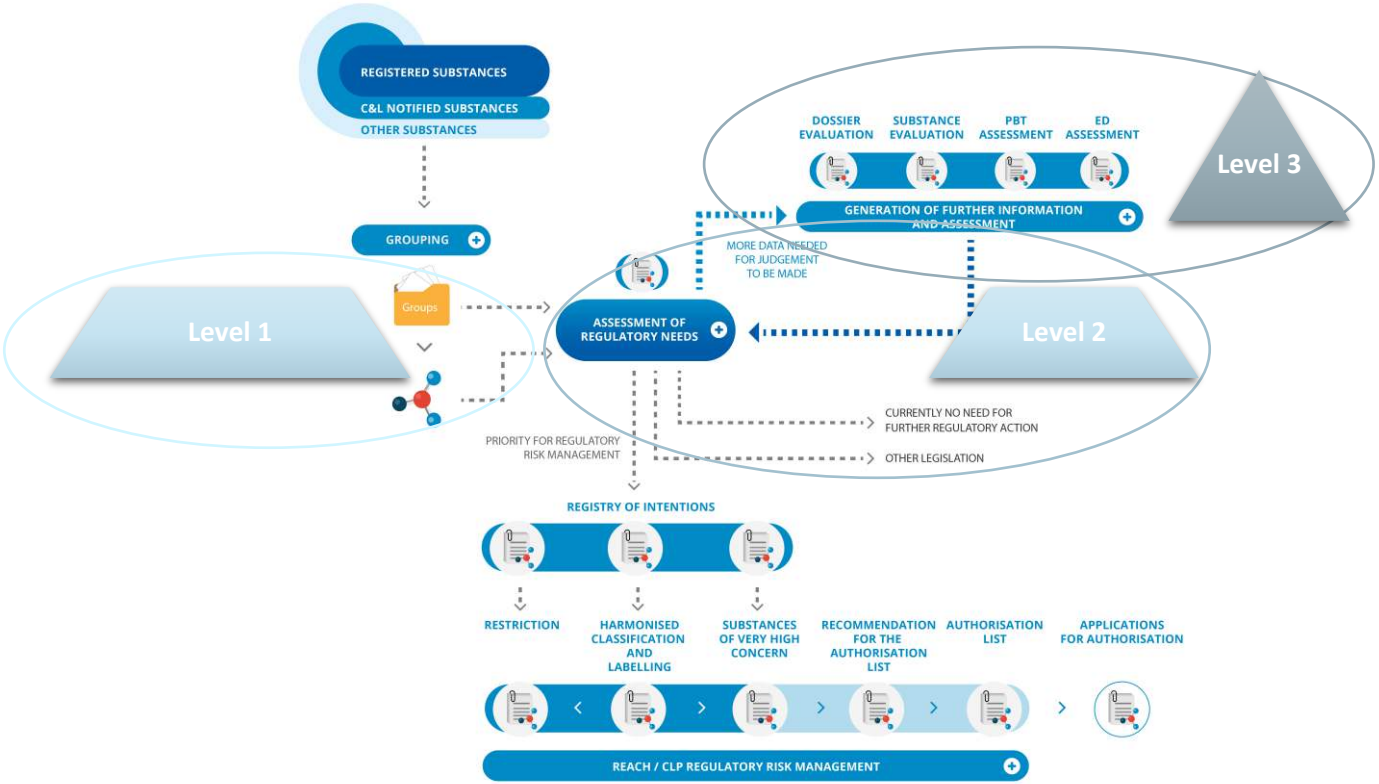


Ad hoc requests where QSAR/NAM expertise is needed
Expert consultations (CCH SEv, GMT),
Assessment of equivalence for biocides
Input to the current grouping work,
Input to CSS, PARC, R&D, etc….

(Semi)automated scenarios to address specific need like an input to GMTs.
Often it requires combination of predictive tools, data and scientific knowledge.

Set of predictive tools and external datasets to be used as building blocs for Level 2-3 (e.g. set of QSARs to predict fate, (eco)tox and TK properties).

The IRS as one example where NAMs are used as input



APCRA Case Studies

APCRA Retrospective Study

TOXICOLOGICAL SCIENCES, 173(1), 2020, 202–225
doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

Katie Paul Friedman ,*,[1] Matthew Gagne,[†] Lit-Hsin Loo,[‡] Panagiotis Karamertzanis,[§] Tatiana Netzeva,[§] Tomasz Sobanski,[§] Jill A. Franzosa,[¶] Ann M. Richard,* Ryan R. Lougee,*,[||] Andrea Gissi,[§] Jia-Ying Joey Lee,[‡] Michelle Angrish,[||] Jean Lou Dorne,[||] Stiven Foster,[#] Kathleen Raffaele,[#] Tina Bahadori,[||] Maureen R. Gwinn,* Jason Lambert,* Maurice Whelan,[**] Mike Rasenberg,[§] Tara Barton-Maclaren,[†] and Russell S. Thomas *

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The primary objective of this work was to compare PODs based on high-throughput predictions of bioactivity, exposure predictions, and traditional hazard information for 448 chemicals.

Of the 448 substances, 89% had POD_{NAM} lower than traditional POD (POD_{trad})

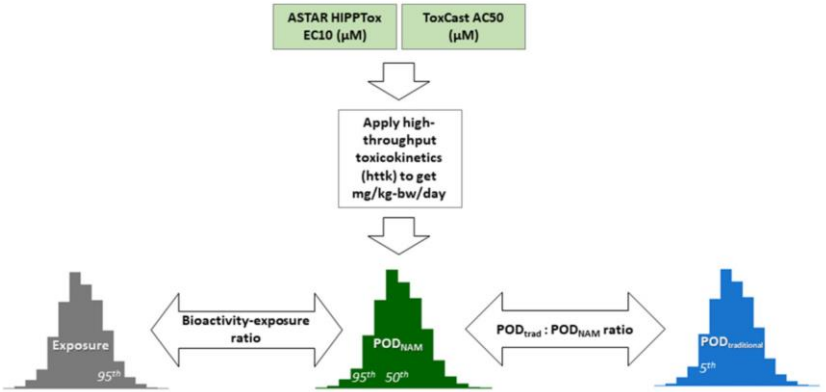


Figure 1. Overall workflow of the case study. This case study includes 448 substances with exposure predictions, *in vitro* assay data, HTTK information using the httk R package, and *in vivo* hazard information. The 50th and 95th percentile from the Monte Carlo simulation of interindividual toxicokinetic variability were used to estimate administered equivalent doses (AEDs), and the minimum of either the ToxCast or HIPPTox-based AEDs were selected as the $POD_{NAM,\ 50}$ or $POD_{NAM,\ 95}$. The POD_{NAM} estimates were compared with the fifth percentile from the distribution of the $POD_{traditional}$ values obtained from multiple sources to obtain the $\log_{10}$ POD ratio. The $\log_{10}$ bioactivity:exposure ratio (BER) was obtained by comparing the POD_{NAM} estimates to exposure predictions. All values used for computation were in $\log_{10}$-mg/kg-bw/day units.

Conclusion: NAM can be already used for (conservative) priority setting

APCRA Retrospective Study further considerations

- This was the largest retrospective look at this to-date, however the protective potential of NAMs have been demonstrated for bioactive chemicals (drugs, pesticides and biocides) with strong MoAs, will it work in a similar way for less potent compounds?
- Specific types of chemicals may be currently outside the domain of applicability due to assay limitations, e.g., organophosphate insecticides: how do we identify these in the future?
- For a significant fraction of investigated chemicals, hazard estimates were over conservative in comparison to systemic in vivo data. Can we improve the accuracy of NAM estimates by consistently applying refined NAM battery?
- Also additional research to include expanded and improved high-throughput toxicokinetics and *in vitro* disposition kinetics may help improve POD_{NAM} estimates.

APCRA Prospective Study
Ongoing work

Prospective Case study is designed around tiered testing framework

Tier 1: *in vitro* screening & *in silico* modelling

Battery of *in vitro* assays, BMD, HTTK, IVIVE

201 substances

Outcomes:
1. Quantitative estimate of *in vivo* POD (LOAEL)
2. Possible insights into hazard profile

FINALISED

- Bioactivity:exposure ratio (BER) to prioritise substances
- Hazard flags to identify concern
- Hazard flags could direct Tier 2 study design

Tier 2: 5-day rodent study

Novel *in vivo* assays using multi-OMICS and BMD

~20 substances

Outcomes:
1. Quantitative *in vivo* POD (LOAEL) based on molecular data
2. Insights into hazard profile

- PODs may trigger Tier 3 testing
- Hazard profile may trigger Tier 3 testing

Tier 3: (if required): more traditional *in vivo* study, depending on hazard profile

NAM-enhanced Test Guidelines (e.g. 90-day RDT with multi-OMICS)

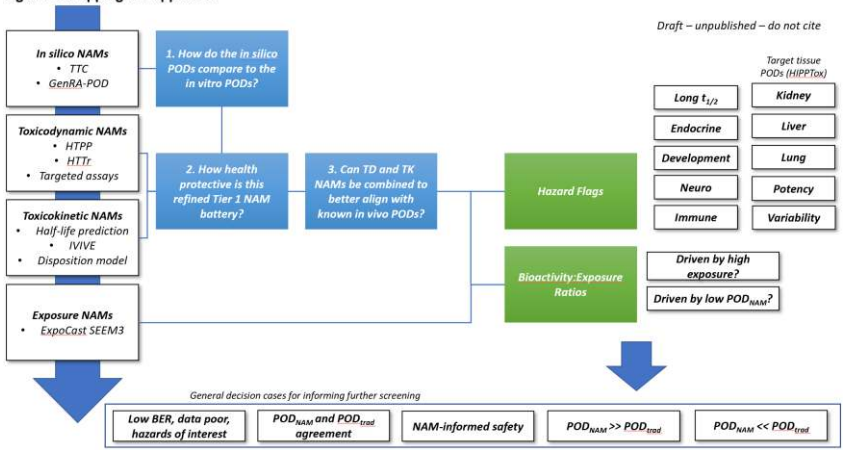
?? substances

Outcomes:
1. Quantitative *in vivo* POD (LOAEL)
2. Hazard profile (CMR, ED, neuro, immuno…)

Could a NAM battery 'mimic' hazard triggers that we would typically also get from a 90-days Repeated Dose Toxicity?

Is the PoD from a NAM battery comparative to PoD from traditional (animal) studies?

Figure 1. Mapping the approach.



Explore how NAMs could give similar information that fits the current system and where are the gaps?

What does it mean for level of protection?

APCRA Prospective Study

What 'comparable with RDT' means for NAMs?

To demonstrate that an outcome is comparable with RDT 90d in the context of hazard characterisation and risk management, NAM testing has to:

✓ Provide estimate of NOAEL and LOAEL:

- NOAEL as potential source for systemic DNEL (if most conservative)
- LOAEL for STOT RE classification

✓ Provide indications/triggers for:

- Toxicity to reproduction
- Immunotoxicity
- Neurotoxicity
- Carcinogenicity
- ED related effects
- Developmental toxicity

Conclusions

- → ECHA is proactive to use NAMs in a Regulatory context, and our activities in this respect are going far beyond the current legal mandate
- → For 'simple' endpoints with local effects, the effort has been focused on in vitro and QSARs, with generally a successful outcome
- → For complex (systemic) endpoints, barriers remain in considering NAMs **as primary input for definitive hazard assessment** under REACH and CLP
- → It is a collective effort and requires buy-in by all stakeholders, including the public

Thank you

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