Nouvelles approches disponibles : perspectives pour les essais alternatifs à visée réglementaire

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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.*

Developing and applying NAMs for regulatory applications

- Overview -

→ Our approach towards 3Rs

→ 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, ASPIS, PARC) and active contribution to APCRA

→ **Making data available**

Publishing information – key for developing new alternatives

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 those in traditional in vivo tests
- some of the current NAMs are over conservative

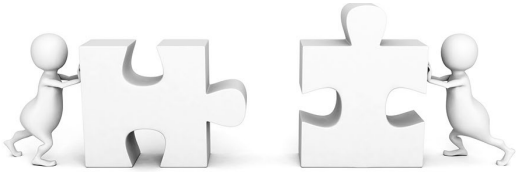
→ New approach methods as standard information requirements:
- Lack of internationally recognised methods
(Mutual Acceptance of Data - MAD)
- Showing added value for the current system not straightforward

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 NAMs 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.

Examples of NAMs for risk assessments

Risk assessment

At ECHA we are using NAMs (mainly broad spectrum of QSARs and High throughput data) as supporting evidence for regulatory decisions under:

→ Dossier Evaluation (REACH):

- to check/replicate registrant's predictions submitted as part of the Registration dossier (i.e. adaptations of the standard information)
- to check whether there is a potential for a given effect (to decide whether to request additional data)

→ Substance Evaluation & Regulatory Risk Management (REACH):

- to support evaluating experts by providing some specific predictions on ADME/TK profile, ED or PBT potential

→ Assessment of Technical Equivalence under Biocidal Products Regulation:

- to predict and compare the hazard profiles of substances produced from a source different to the reference source

APCRA Retrospective Study

OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight article

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

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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})

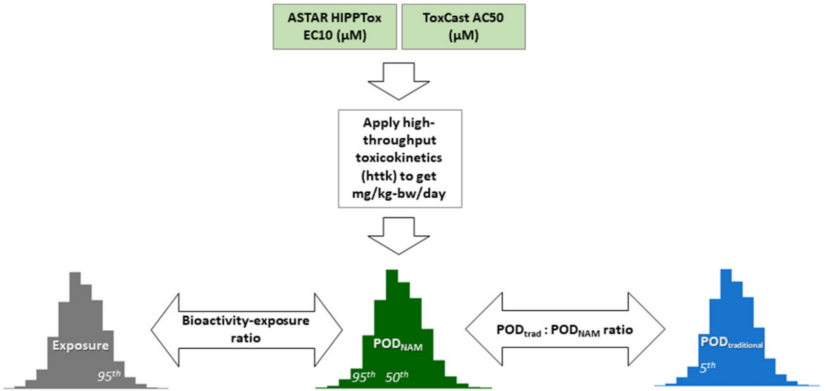


Figure 1. Overall workflow of the case study. This case study includes 448 substances with exposure predictions, *in vitro* assay data, HTTK information using the httk R package, and *in vivo* hazard information. The 50th and 95th percentile from the Monte Carlo simulation of interindividual toxicokinetic 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 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)

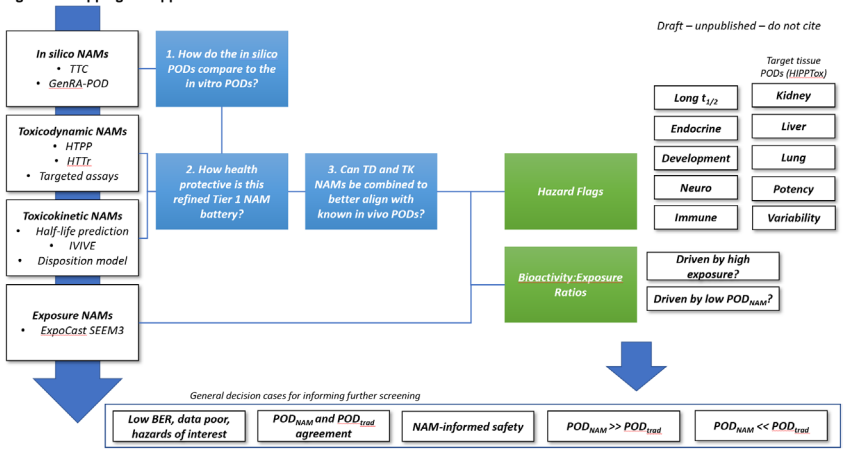
?? substances

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?

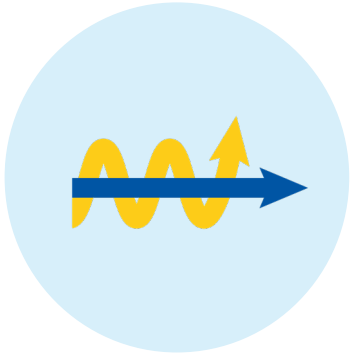
Summary

- → Regulatory challenges: the current regulatory system is designed with traditional, including animal, tests
- → Scientific challenges: complexity makes the development of one-to-one replacements difficult
- → Short-term opportunities exist to better integrate NAMs in the current system
- → Long-term: full replacement requires advancement in science and policy changes
- → Our next 117.3 report will illustrate our efforts to promote NAMs and discuss the collaboration with EC to propose a NAM roadmap (towards an animal-free system)

Articulating ECHA's work to promote NAMs and alternatives to animal testing

Effective implementation of the IRS to identify and address risks of chemicals of concern

Investment in international activities promoting alternatives



Making data available

It is a collective effort and requires buy-in by all stakeholders

ECHA
EUROPEAN CHEMICALS AGENCY

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