Experience of ECHA in applying NAMs in a regulatory context

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Do you or your organisation apply New Approach Methodologies (NAMs) for risk assessment in regulatory toxicology and, if so, which methods do you use for which purpose?

At ECHA we are using NAMs (mainly broad spectrum of QSARs and ToxCast/Tox21 assays) 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

Are you planning to expand these applications or to introduce other NAMs in the near future?

Currently we are running pilot projects to extend the application of NAMs at the group assessment level and for addressing low tonnage substances where less information is available

We are adding new tools once available to us, mainly computational methods as we don't develop NAMs nor generate ourselves experimental data for the assessment of registered substances

For 'omics we are broadly investigating the utility of these technologies as supporting evidence in regulatory decision making as well as in deriving PoD (APCRA and EUToxRisk case studies)

ECHA is also actively supporting efforts related to:

- ✓ development and implementation of the new TGs and DAs
- ✓ development of the OECD QSAR Toolbox
- ✓ development of the new validity criteria for *in silico* predictions
- ✓ development of reporting standards (OECD TRF and MFR reporting frameworks)
- ✓ demonstrating reproducibility of omics technology (CEFIC MERIT project) and
- ✓ investigating the toxicological relevance of metabolomic biomarkers (M700+ project)

APCRA retrospective case study

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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.

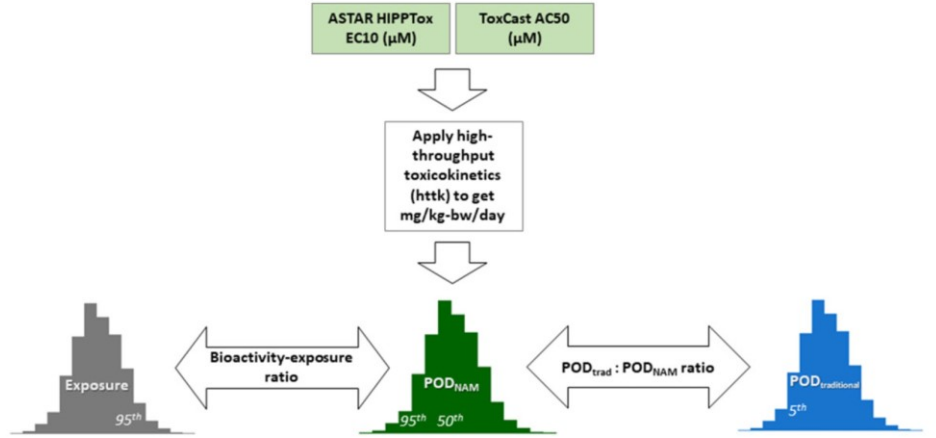


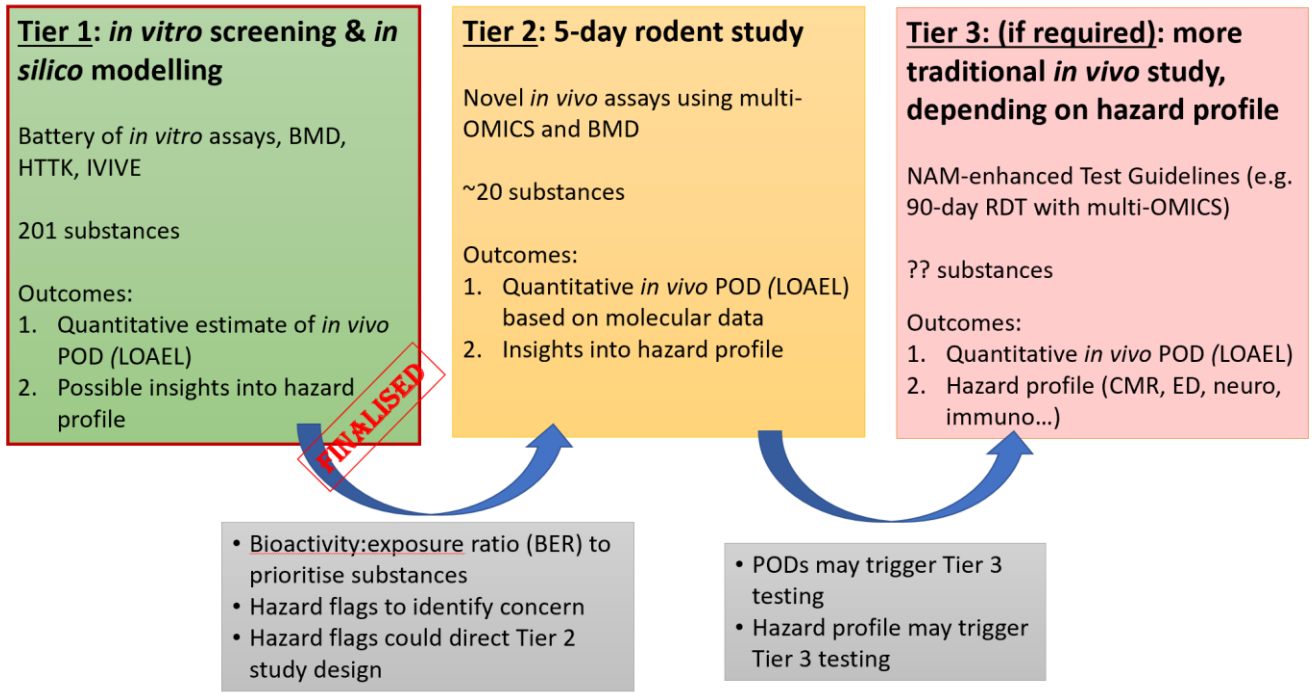
Figure 1. Overall workflow of the case study. This case study includes 448 substances with exposure predictions, *in vitro* assay data, HTTK information using the httk R package, and *in vivo* hazard information. The 50th and 95th percentile from the Monte Carlo simulation of interindividual toxicokinetic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

Of the 448 substances, 89% had a POD_{NAM}, estimates were lower than the traditional POD (POD_{TRAD}) value

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

APCRA prospective case study (ongoing)

Prospective Case study is designed around tiered testing framework



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

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

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?

To conclude:

ECHA is proactively searching for an opportunities 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, we see significant barriers in considering NAMs **as primary input for definitive hazard assessment** under REACH and CLP, the main difficulties are:

- Information requirements in REACH refer to animal tests, and often to a specific OECD in vivo test guidelines, indicated in the REACH Annexes.
- REACH provisions for adaptations of the standard information requirements which assume an **equivalence in level of information and suitability for RA and C&L**
- the spectrum of observed effects in systemic endpoints is very wide: clinical observations, haematology and clinical biochemistry, pathology, gross necropsy, histopathology. NAMs cannot replicate (or provide equivalence) for this wide spectrum of effects
- NOAELs and LOAELs are based on observed adverse effects, there is a limited number of NAMs able to directly predict adverse outcome, and those available can cover only a limited number of effects included in the in vivo study
- NAMs are very useful co confirm or support hypothesis about MoA, however reality for industrial chemicals is that often there is no such knowledge/data available


Thank You
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