JRC Survey on NAMs

EPAA “Deep-dive” workshop: Use of NAMs in regulatory decisions for chemical safety

23 November, 2021
Extending REACH Information Requirements - overview

- Action led by JRC with support of steering group (DG ENV, DG GROW, ECHA)
- Annexes VII to X: standard information requirements, largely tonnage-dependent
- Annex XI: general rules for adaptation:
  - existing data, QSAR, grouping & read-across, WoE, exposure-based considerations
- Introduction of Chemical Safety Assessment at Annex VII (instead of Annex VIII)
- Inclusion of critical hazards at Annex VII
  - carcinogenicity, mutagenicity, reproductive toxicity, endocrine disruption, neurotoxicity, respiratory sensitisation, immunotoxicity, and other specific target organ toxicity, persistent, bioaccumulative and toxic
- Options to be subject to Impact Assessment before COM adopts legislative proposal
Extending REACH Information Requirements - survey

• Aimed primarily at method users

• Emphasis on practical applicability / deployability

• NAM-based strategies that have the potential to fulfil one or more of the following regulatory needs:
  1. Derivation of a DNEL (Derived No Effect Level) for use in a human health risk assessment
  2. Derivation of a PNEC (Predicted No Effect Concentration) for use in an environmental risk assessment
  3. Classification and Labelling
  4. PBT or vPvB assessment
  5. Assessment of a critical hazard (including those not covered by 3 or 4)

• Open since 25 June
Responses as of 24-11-21

- 75 responses (NAMs) via EUSurvey Tool, including some duplicates (e.g. Next Generation Risk Assessment; IATA for fish toxicity).

- Responses from:
  - Unilever, P&G, L’Oreal, Sun Chemical, Shell, Evonik, Concawe, Corteva
  - Environment and Climate Change Canada, US EPA, Norwegian Institute of Public Health, INRAE
  - ICATM partners: JaCVAM
  - Several academic institutions
  - Several consultancies / SMEs
  - Non-profit: HESI

- 11 separate responses from Cosmetics Europe

- SCCS – list of dossiers in which NAMs were used

- 74 NAMs from EU ToxRisk (received on 15-10-21)
EU Survey responses as of 24-11-21: 75 responses

Reasonable endpoint coverage:
- Skin sensitisation, skin irritation, eye irritation, physicochemical properties
- Aquatic toxicity (fish, daphnids, algae), bioaccumulation and persistency
- Genotoxicity
- Acute systemic toxicity
- Other STOT (liver, kidney, cardiotoxicity)
- Developmental / reproductive toxicity
- Respiratory irritation

Still poor coverage:
- Carcinogenicity
- Immunotoxicity
- DNT
- Endocrine (HH and ENV)
- ADME
- Respiratory sensitisation
EU ToxRisk responses: 71 NAMs

EU ToxRisk NAMs

<table>
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<tr>
<th>Category</th>
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**CONCLUSION**

| Sufficiently mature to (partially) fulfil information requirement (annexes VII-X) | X |
| Potential to (partially) fulfil information requirement (in next 3 years) | |
| Suitable for use in Annex XI adaptation | |
| Not ready or relevant for regulatory use | X |

Some examples

Response 11

- **Title**: Machine-learning and predictive modelling
- **Type**: physicochemical, in silico, in vitro, other, hybrid (combination of different types of methods)
- **Brief description. Mention all component methods and explain how they are integrated**: Good quality data - whether tox and/or biological. If the datasets are huge, capability in high performance computing (HPC).
- **Are you using it in-house, or do you intend to do so, for a practical application?**
  - Yes
  - No
- **If yes, briefly explain the current or intended application**: Diagnosis of infectious diseases, and pathway identification.
- **Potential regulatory applicability**
  - Establish a point of departure for use in DNEL derivation
  - Establish a point of departure for use in PNEC derivation
  - Classification and Labelling
  - PBET or vPvB assessment
  - Assessment of a critical hazard
- **Type of output(s). Please also specify the endpoint(s)**
  - Categorical (e.g. toxic/non-toxic)
  - Ordinal (e.g. high/medium/low toxicity)
  - Quantitative (continuous scale)
- **Endpoint(s)**
  - In vitro LD50 - cell viability via tritiated thymidine, MTT etc assays
CONCLUSION

Sufficiently mature to (partially) fulfil information requirement (annexes VII-X)

Potential to (partially) fulfil information requirement (in next 3 years)

Suitable for use in Annex XI adaptation X

Not ready or relevant for regulatory use
**CONCLUSION**

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Next Generation Risk Assessment (NGRA) is defined as an exposure-led, hypothesis-driven risk assessment approach that integrates New Approach Methodologies (NAMs) to assure safety without the use of animal testing. It is based on the concept that NAMs can be used to identify exposure levels that are protective of potential adverse health effects in humans, either in the context of exposure in a consumer or occupational setting, or for the environment. The premise of NGRA is that if in vitro bioactivity is not seen in a suitable test panel at human/environmentally-relevant concentrations, then the risk of adverse effects is negligible. As in any safety assessment, successive refinements are possible to increase certainty in the outcome. As a starting point, in-silico tools are used to generate predictions on hazard alerts and physicochemical properties. Tools used include ToxTree, exposure-based waiving (Yang et al, 2017), OECD Toolbox, Derek Nexus, VITIC, Meteor Nexus, TIMES, and molecular initiating events (MIE) ATLAS (Allen et al).

In the event that non-testing approaches are not sufficient to determine safety, the next level of refinement involves determining a Bioactivity Exposure Ratio (BER), which quantifies the differences between relevant internal exposure levels (e.g. Cmax) in humans or environmental species (given the use case of the chemical) and the concentration required to trigger bioactivity in in-vitro assays (Baltazar et al, 2020) in terms of points of departure (PoDs). Bioactivity assays include the cell stress panel (Hatherell et al, 2020), high-throughput transcriptomics (Harrill et al, 2021) and in vitro pharmacological profiling (e.g. Eurofins Cerep 44). All assays involve generating concentration-response data and PoDs can be estimated from the data using different approaches: BMDxpress (Phillips et al, 2019), Gaussian process regression (Reynolds et al, 2020), TCPL2.0 (Harrill et al, 2021).

The effect of metabolism on the bioactivity of the compound (e.g. through the formation of toxicologically relevant metabolites) is most effectively addressed using metabolically competent cell models to form metabolites in situ to ensure transient or reactive metabolites reach the sites of concern. Alternatively, in vitro assays can be supplemented with sub-cellular fractions (e.g liver microsomes or S9) to metabolise the test chemical within the assay or metabolites can be produced externally (by chemical or biological means) and added at dosing.
Sufficiently mature to (partially) fulfil information requirement (annexes VII-X)
Potential to (partially) fulfil information requirement (in next 3 years) X
Suitable for use in Annex XI adaptation
Not ready or relevant for regulatory use
Overall evaluation of EU Survey responses

- 53: Sufficiently mature to (partially) fulfil information requirement (annexes VII-X)
- 14: Potential to (partially) fulfil information requirement (in next 3 years)
- 7: Suitable for use in Annex XI adaptation
- 1: Not ready or relevant for regulatory use