Making sure that NAM-based safety assessments are protective

Matt Dent

Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire MK44 1LQ;
Outline

1. Why do we have confidence that *in vivo*-based risk assessments are protective?
2. Can this inform our approach to NAM-based assessments?
Why are we confident that animal-based assessments are protective?

Important to remember that animal tests are not necessarily predictive of adverse health effects in people – but used in a certain way they are useful for making safety decisions.
So how do we build confidence that NAM-based assessments are protective?

Familiarity
- Evaluating strengths and limitations of NAMs; training

Regulatory guidance/precedent
- Examples of NAM-based decision making

Standardized protocols
- Agreed protocols, analysis and reporting standards, future of validation

Important to remember that *in vitro* tests are not necessarily predictive of adverse health effects in people – but *used in a certain way* they are useful for making safety decisions.
So how do we build confidence that NAM-based assessments are protective?

Important to remember that *in vitro* tests are not necessarily predictive of adverse health effects in people – but *used in a certain way* they are useful for making safety decisions.

**Familiarity**
- Evaluating strengths and limitations of NAMs; training

**Regulatory guidance/precedent**
- Examples of NAM-based decision making

**Standardized protocols**
- Agreed protocols, analysis and reporting standards, future of validation?
APRCA approach to evaluate the integration of exposure and bioactivity

- Evaluation of in vitro NAMs, exposure modelling and dose-response models.
- For 89% of the chemicals NAM PoD was more conservative than the traditional POD.
- Bioactivity:exposure ratios (BERs) approach useful for accelerate screening and assessment using NAMs for hazard and exposure.

Confidence in skin allergy NGRA - Unilever SARA Model

NAMs mapped into the AOP

Bayesian computational model that integrates information from the historical data and NAMs

SARA Model published and collaboration with US Gov. group (NICEATM) to adapt the model for regulatory use.
The key NAMs in our Systemic NGRA approach

PBK Modelling

In vitro pharmacological profiling

Transcriptomics

- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7
- 3D HepaRG spheroid

BMDexpress 2

Toxicology in Vitro (2020), 63, 104746

Cellular Stress Pathways

13 chemicals, 36 Biomarkers; 3 Timepoints; 8 Concentrations; ~ 10 Stress Pathways
Exposure and PoD are plotted and used to derive a Bioactivity-Exposure Ratio (MoE/BER)

How can we evaluate this NAM-based approach to ensure we can make robust safety decisions that are at least as protective as traditional approaches?
Overview of the toolbox evaluation strategy

Stage 1: Define benchmark chemical-exposure scenarios

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Exposure scenario</th>
<th>Risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem X1</td>
<td>Scenario Y1</td>
<td>High</td>
</tr>
<tr>
<td>Chem X2</td>
<td>Scenario Y2</td>
<td>Low</td>
</tr>
</tbody>
</table>

Stage 2: Apply NAM tools to generate bioactivity and exposure data for POD and $C_{max}$ estimates

Stage 3: Estimate minimum platform POD and population average $C_{max}$ to calculate the BER

Stage 4: Benchmark BER against risk category for each exposure scenario in Step 1

Can the toolbox correctly identify the risk classification?
Stage 4 - Benchmark BER against risk category for each exposure scenario in Step 1

Centred 50% and 95% credible intervals summarising the distribution of the BER when using all available predicted $C_{\text{max}}$ estimates. Background colours indicate the assigned risk category for each benchmark exposure (blue – low, orange – high).

Testing 40+ chemicals using the same approach

Further iterations to ensure toolbox protective
Conclusion & Next steps

• The first step in building confidence that NAM-based assessments can be protective is to build familiarity – understanding the strengths and weaknesses of the technology.

• Without evaluations like this NAM-based assessments will always be viewed with suspicion.

Familiarity
Evaluating strengths and limitations of NAMs; training

Regulatory guidance/precedent
Examples of NAM-based decision making

Standardized protocols
Agreed protocols, analysis and reporting standards, future of validation?
Recognition of NGRA in cosmetic safety assessment...

...Could we apply similar approaches to chemical registration?

A framework for chemical safety assessment incorporating new approach methodologies within REACH

Nicholas Ball¹ · Remi Bars² · Philip A. Botham³ · Andreea Cuciureanu⁴ · Mark T. D. Cronin⁵ · John E. Doe⁶ · Tatsiana Dudzina⁶ · Timothy W. Gard⁷ · Marcel Leist⁸ · Bennard van Ravenzwaay⁹

European Commission: Scientific Committee on Consumer Safety (2021)
Acknowledgements

Maria Baltazar, Alistair Middleton, Sophie Cable, Joe Reynolds, Hequn Li, Predrag Kukic, Paul Carmichael, Beate Nicol, Sharon Scott, Sophie Malcomber, Annabel Rigarlsford, Chris Sparham, Trina Barritt, Katarzyna Przybylak, Georgia Reynolds, Andrew White, Sarah Hatherell, Richard Cubberley, Carl Westmoreland