Safety & Environmental Assurance Centre

Building confidence in using new approach methodologies for consumer-based risk assessment: challenges and future perspectives

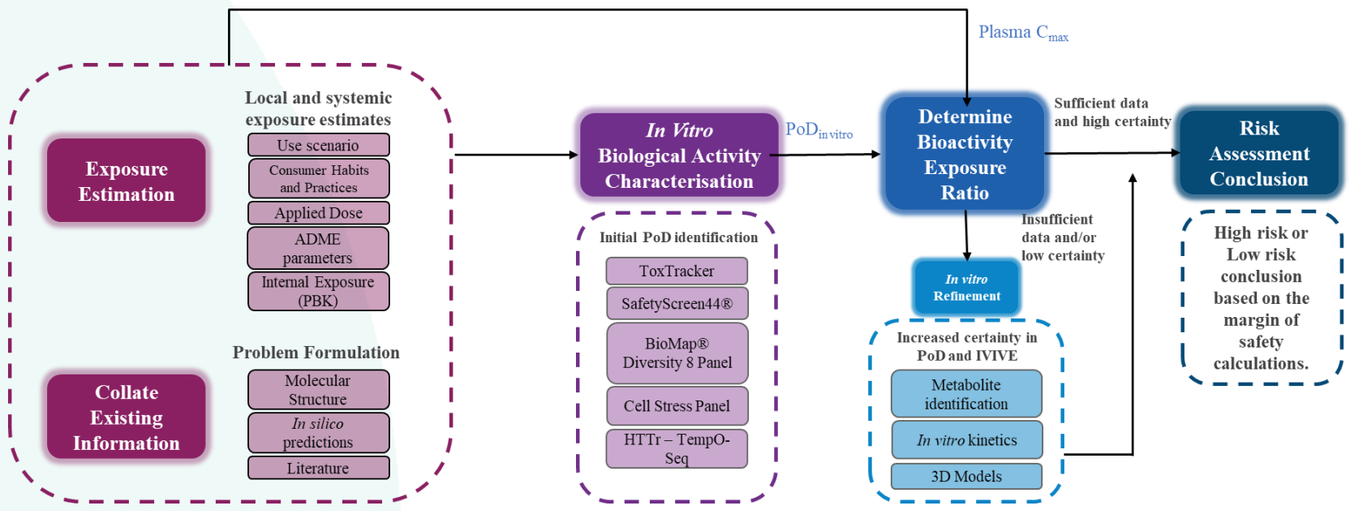
Alistair Middleton, George Fitton, Tom Moxon, Andrew White, Maria Baltazar, Ramyarooban Kanapathywasam, Cameron Mackay
Unilever Safety and Environmental , Sharnbrook, United Kingdom

Introduction

Using the risk assessment of 0.1% coumarin in a face cream and body lotion as an exemplar case study, we recently demonstrated how new approach methodologies (NAMs) can be applied in Next Generation Risk Assessment (NGRA) to assess the safety of consumer product ingredients [1]. While this study helps build confidence in the use of NAMs for consumer-based risk assessments, there is an on-going need to demonstrate that these approaches can be used to define low-risk consumer exposures for a wider range of chemicals, exposure scenarios and endpoints. In particular, the various NAMs used in the coumarin case study represent a **toolbox** that could be used in risk assessment more broadly. We are currently **evaluating** this approach by generating analogous NAM data for a wide range of different compounds and exposure scenarios that can be used for **benchmarking**. In general, the use of NAMs in NGRA are critically dependent on being able to **integrate computational modelling approaches with in-vitro assay data** in a robust manner. Being able to do this with confidence hinges on two key areas: ensuring that the **data analysis methods** are **reproducible and transparent** [8,9], and **using robust scientific methods** to evaluate the NAMs from **decision-making perspective.** The former is analogous to **GLP** used to generate the in-vitro data. The latter relates to ensuring NAMs can be combined in such a way that they lead to decisions that are **protective of human health** where any uncertainties are characterised in an appropriate manner [2].

Coumarin case study: integrating models and data to make safety decisions with confidence

- NGRA relies on the integration of *in vitro* assay data and computational models to aid safety decision making.
- *In silico* tools are used to are used to obtain initial exposure estimates and identify potential hazards
- Physiologically based kinetic (**PBK**) models are used to estimate internal exposure levels such as **Cmax**.
- Concentration response data are used with modelling approaches to estimate points of departure (**PoD**).
- A key decision metric is the Bioactivity Exposure Ratio (**BER**).



Robust science for decision-making

Benchmarking NAM-BERs against historical safety decisions
How can we ensure that the BER can be used to defined exposure levels are that protective of human health? This requires **human-relevant** data to benchmark the BER against. The approach used in Hatherell et al. [3], where chemical-exposure scenarios drawn from a set of well-documented safety decisions made using traditional approaches, can be used more generally to assess if the NAM-BERs generated by the toolbox are sufficiently protective of human health.

Quantification of uncertainties
Each NAM will have some **uncertainties** associated with it. Is there sufficient biological coverage of the assays? How can we be confident that we are correctly detecting PoDs from the data? How can we be confident that our PBK models provide a good estimate of the Cmax? Addressing these issues requires appropriate data to evaluate the approaches against, together with robust statistical analysis methods. **Bayesian statistics** for example provides a framework to quantify these uncertainties in a systematic manner (see [3-6]).

Defined applicability domain
Evaluating the toolbox against appropriate benchmark data will make it possible to identify **potential gaps** and define what the applicability domain of the toolbox may be and how it could be **extended**.

Reproducible and transparent data analysis

Digital Transformation
Robust science for decision making is founded on **FAIR data** [7] (findability, accessibility, interoperability, and reusability), **robust scientific code** [8] (test driven, e.g., TDDA [9]), and **transparency** (open-source collaboration). Building software and tools that support increasingly complex mathematical models that support NGRA, which are connected to larger and larger (human relevant) datasets, requires close collaboration between risk assessors and experimental scientists and, importantly, the data scientists who implement the analysis in scientific software. SEAC is taking this challenge head-on, investing heavily in its Digital Transformation.

Robust and Reproducible Data Analysis
There are two key challenges in SEAC's digital transformation: building trust in scientific software (and the results they produce for decision making) and being able to build and maintain robust risk assessment software. Trust in code and data starts with **version control** and **provenance** (change history and tracking at every step). Future proofing and robustness are guaranteed with test-driven development [10]. Finally, adoption of technologies such as Models-as-a-Service can enable re-usability, scalability and reproducibility of data processing and analyses methods [11].

Transparency
Broad adoption of these approaches necessitates open-source science and collaboration. Transparency is key to building confidence in new methods. Taking an open-source software approach to data-analyses and, more generally, an open science approach to new methods for consumer risk assessment can facilitate this.

Conclusions and Future Work

- Transparency is key to building confidence in new methods. This requires:
  - collaborative and open-source scientific software that promote sharing code to facilitate peer review
  - Open data i.e. ability to easily share, search and analyse data.
- Benchmarking against historical safety decisions can provide systematic approach for evaluating the use of NAMs in risk assessment.
- Addressing uncertainty in NAM outputs is a key aspect of ensuring the decision-making process is robust. Approaches such as Bayesian statistics provides a natural framework to quantify these uncertainties in a transparent and systematic manner.

References

[1] Baltazar, et al. Toxicological Sciences 176.1 (2020): 236-252.
[2] Dent et al. Computational Toxicology 7 (2018): 20-26.[2]
[3] Hatherell et al. Toxicological Sciences 176.1 (2020): 11-33.
[4] Reynolds et al. Computational Toxicology 9 (2019): 36-49.
[5] Reynolds et al. Computational Toxicology 16 (2020): 100138.
[6] Guidance on Uncertainty Analysis in Scientific Assessments
[7] FAIR Principles
[8] Aruliah, Best Practices for Scientific Computing (2012)
[9] http://www.tdda.info/
[10] Kent, Test-driven development: by example (2003)
[11] Models-as-a-Service Using Cloud Services Innovation Platform