Safety & Environmental Assurance Centre

The application of advanced tools in Next Generation Risk Assessment (NGRA) of cosmetics ingredients

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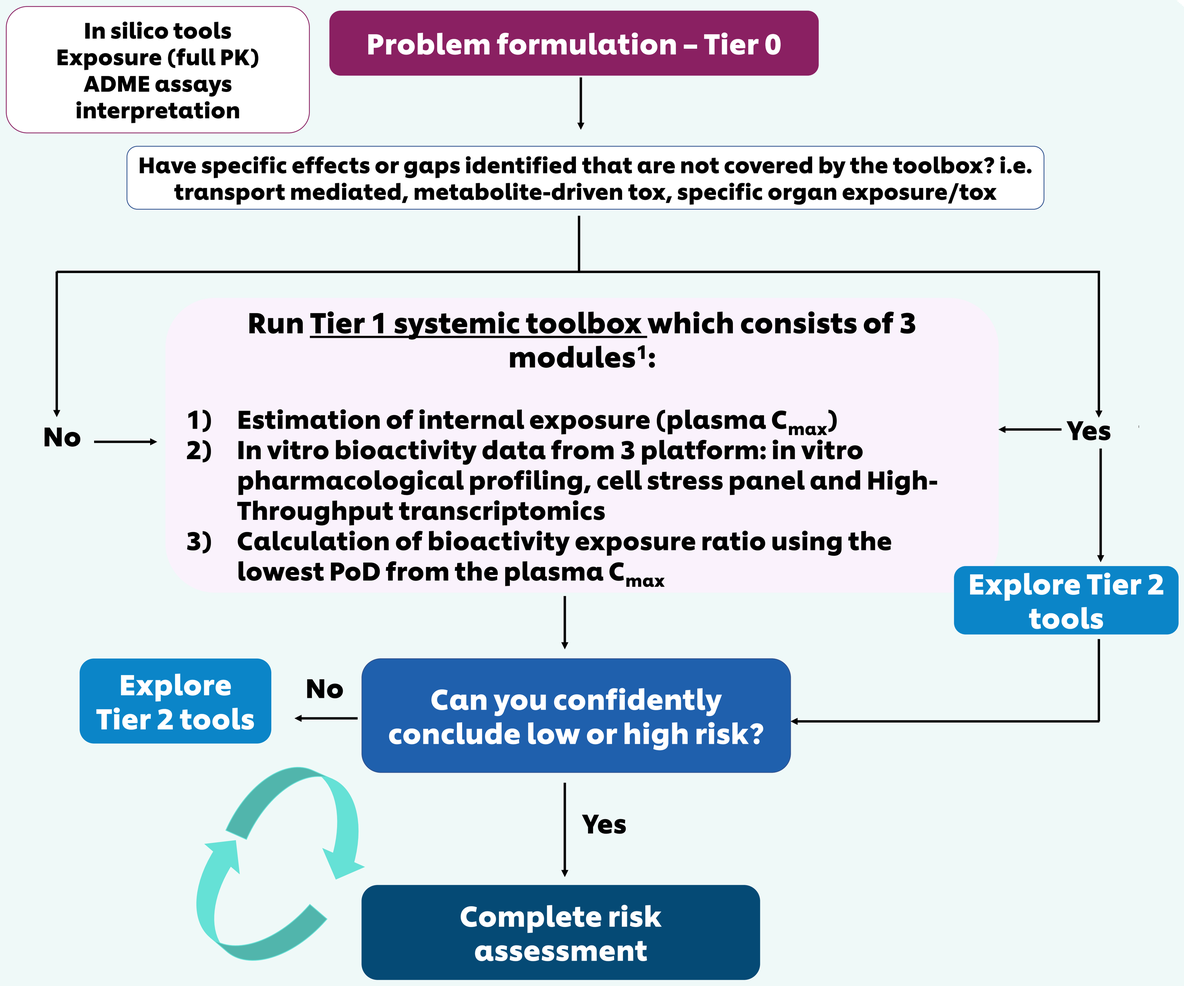
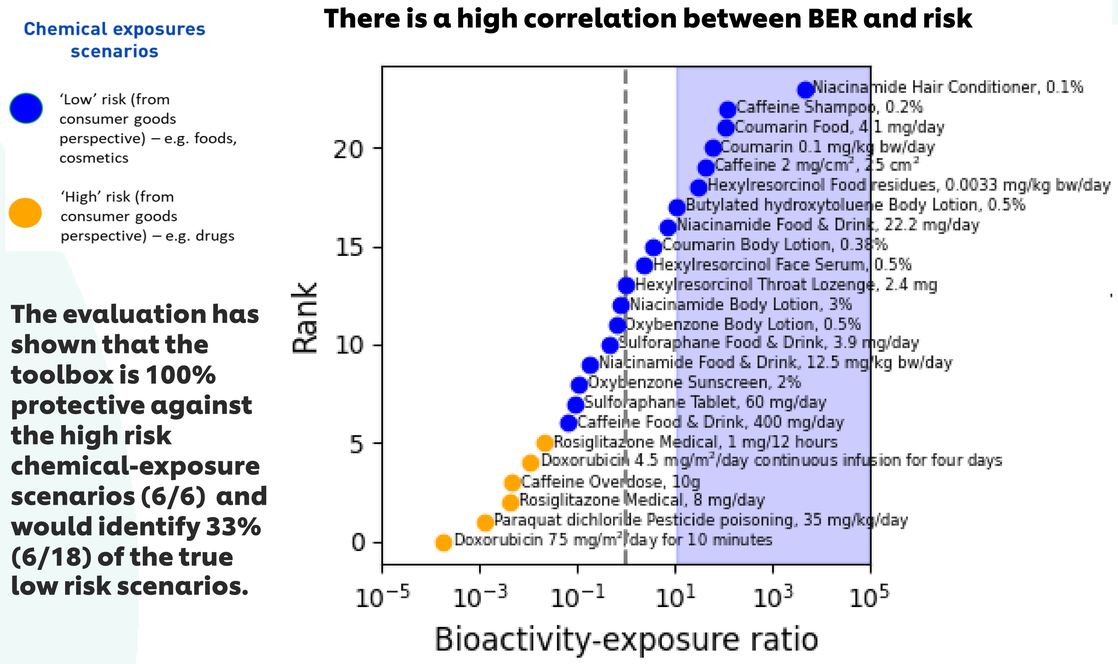
Introduction

For systemic safety, early tier tools showed promise for use in a protective rather than predictive capacity but demonstrated that the tier 1 might be overly conservative given that measures of chemical potency are based on bioactivity, which may not necessarily translate into adverse effects in humans[1,2,3]. Therefore, advanced organ models, including microphysiological systems (MPS) have the potential to be used as a refinement tool when a decision with a low tier approach could not be made. The potential areas of application of MPS in NGRA include both the use of individual organ systems (e.g. explore specific mechanisms of toxicity or transport mediated-toxicity) and multiorgan-on-a-chip to investigate kinetics, metabolism and organ-to-organ communication (e.g. endocrine system).

Tiered and exposure-led framework for systemic safety



Tier1: Initial evaluation of the performance of the systemic toolbox[3]



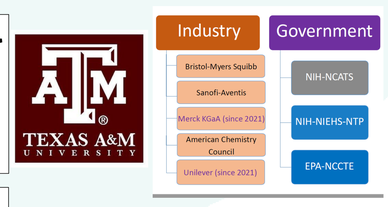
The evaluation has shown that the toolbox is 100% protective against the high risk chemical-exposure scenarios (6/6) and would identify 33% (6/18) of the true low risk scenarios.

Figure 1. The evaluation of the NAM toolbox was performed using 24 exposure scenarios from 10 chemicals, some of which would be considered high risk from a consumer goods perspective (e.g., drugs that are systemically bioactive) and some low risk (e.g., existing food or cosmetic ingredients). BER is determined by the ratio between lowest POD and the plasma C_{max} for the corresponding exposure scenario. In this plot the C_{max} was derived from a PBK model parametrised with mostly in vitro-derived parameters. Chemical-exposure scenarios with a bioactivity-exposure ratio (BER) point estimate outside the blue-shaded region would be identified as "uncertain" risk under this decision model. The gray-dashed line corresponds to BER = 1. This work will enable a full evaluation to assess how protective and useful the toolbox and workflow are across a broader range of chemical-exposure scenarios. Furthermore, this pilot study has identified important limitations of the NAMs used, which can be addressed in future iterations of the toolbox.

Tier 2: ongoing collaborations developing and evaluating advanced models and MPS

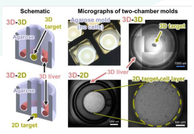
TEXVAL consortium- Evaluation of Microphysiological Systems (MPS) for a range of organs and devices[4]

- Gut, liver, kidney, Blood-brain-barrier
- Mimetas & CN-BIO vs 2D and 3D cultures



Implementation of a Human Liver 2 Compartment Metabolizing System

- Two-chamber liver-organ co-culture model in a higher-throughput 96-well format for the determination of toxicity on target tissues in the presence of physiologically relevant human liver metabolism (Ip B et al submitted)



Evaluating Integrated Flow System for toxicity testing – liver chip using the Mimetas system[5]

- Culture of HepaRG in Mimetas vs plates
- Chemical distribution in MPS device
- Investigation of cholestasis

Drug risk assessment and repurposing using biomimetic chromatography and body-on-chip technology

- Hypothesis: Body-on-chip platforms capable of circulating drug loaded plasma across the organ compartments can provide PK/PD data consistent with that of gold standard in vivo human PET data for the same drug.

Lung on a chip: Alveolix partnership

- Evaluation of a lower airway model to test inhaled cosmetics ingredients
- Comparison of advance and physiologically closer models with simpler models such as A549 cells on transwell

Tier 2: Case studies to identify useful tools to refine risk assessment

Example with Caffeine in foods and drinks exposure scenario

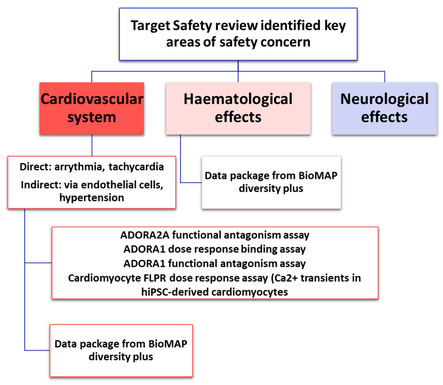
1. Context:

- Toolbox prediction of **uncertain risk (BER=0.18; Figure 1))**.
- The lowest toolbox PoD for caffeine is **adenosine A2A receptor binding in In vitro Pharmacological Profiling panel (IPP) (Eurofins)** (5.3µM). No other adenosine receptors isoforms are included in IPP.

2. Problem formulation:

- Conduct a target safety review: what is the physiological role of the target? Where is this target expressed? What are the biological interactions and pathways that this target is involved in? What are the toxicological adverse outcomes excepted?

3. Mapping of the next testing strategy: the literature review identified cardiovascular, haematological and neurological effects as the key safety areas



4. Focus on cardiovascular system and use a benchmark approach to define a threshold of toxicity based on functional assays:

- Comparison to other methylxanthines in foods and drugs:
  - Theophylline
  - Pentoxifylline
  - Theobromine
  - Others?
- Drugs developed as antagonists of A2A?
- Based on this approach could we support the level of caffeine in energy drinks?

References

1. Baltazar MT et al., (2020). Toxicol Sci;176(1):236-252.
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3. Middleton AM et al., (2022) Toxicol Sci. 189(1):124-147.
4. Rusyn I et al., (2022). Toxicol Sci; 188 (2): 143–152.
5. Nitsche KS et al., (2022). Arch. Toxicol 96(3):711-741

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