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Poster

NEW INSIGHTS IN READ ACROSS USING NEW APPROACH METHODS

C. Mahony[1], C. Alexander-White[2], D. Bury[3], M. Cronin[4], M. Dent[5], N.J. Hewitt [6], G. Kenna[6], J. Naciff[7], G. Ouedraogo[3], A. Schepky[8]

[1] Procter & Gamble Technical Centres Ltd, Reading, UK; [2] MKTox & Co Ltd, Milton Keynes, UK; [3] L'Oreal Research & Innovation, Clichy, France; [4] School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK; [5] Unilever, Safety & Environmental Assurance Centre, Sharnbrook, Bedfordshire, UK; [6] Cosmetics Europe, Brussels, Belgium; [7] The Procter & Gamble Company, Cincinnati, OH, USA; [8] Beiersdorf, Front End Innovation, Hamburg, Germany

In the context of Read-Across (RAX), new approach methods (NAMs) can help to strengthen the identification of suitable substances for RAX, increasing confidence in the analogue identification and the no observed adverse effect level (NOAEL) used as a point of departure (PoD) in a Next Generation Risk Assessment (NGRA). NAMs have also been used to inform on relative potency of analogue mode of action (MoA) and to predict internal exposure in both human and animal studies allowing for a risk assessment approach based on internal exposures without need to account for inter-species kinetic variability. To facilitate the implementation of RAX in a regulatory context, a framework to organise and report the information is needed to enable transparent, reproducible and scientifically defensible decision-making. We outline a 10-step framework for cases where a Threshold of Toxicological Concern (TTC) approach is not possible as exposure levels are not sufficiently low.

10-Step RAX framework

Tier 0

Step 1: Identify exposure/use scenarios for target chemical

1. Exposure estimates - start with rough deterministic estimation at the low tier and evolve to more complex subject-orientated probabilistic approach at higher tiers (e.g. as per SCCS Notes of Guidance, 10th Revision SCCS/1602/18)

Step 2: Identify molecular structure of target chemical

2. Review full composition of raw material, including any potential low-level impurities. Summarise structural features of the target chemical by identifying molecular scaffolds or substructures, substituents, functional groups, tautomeric forms, and alkyl chain lengths. Identify known or likely biotransformations for the target chemical, identifying any potential for reactive metabolite formation.

Step 3: Collate supporting data on target chemical and define data gap(s)

3. Collate physicochemical data, toxicological, ADME and existing NAM information. **Define problem formulation and identify data gap**

Can go back to start of **Step 4** to broaden or narrow analogue selection/revisit analogue search strategy based on outcome of analysis of existing data set.

Step 4: Analogue(s) a) Identify, b) collate existing data, c) determine similarity hypothesis

4. Using structural features from **steps 2 & 3**, describe analogue search strategy based on: (sub)structures, metabolism, reactive chemistries, physicochemical properties and functional groups i.e. (sub)structures, functional groups, metabolism. Define chemical (e.g., Tanimoto) similarity comparisons of molecular fingerprints plus searching by substructure with required structural features. Include an analysis of concordance of data between target and analogue(s); **Derive a hypothesis of mechanism of action for target and analogues in terms of the effect to be assessed by RAX** (e.g., low/no toxicity; parent versus metabolite-mediated toxicity)

N.B. If no analogues or there are analogues but no data are identified, RAX is not possible and another safety assessment strategy should be considered

Analogues but insufficient data to be confident – Progress to **Tier 1**

Describe rationale for generating additional ADME and MoA information

Tier 1

Step 5: Supporting similar bioavailability/ ADME of target chemical and analogues

5. Data to inform on similar ADME properties: e.g., skin and gut permeability; plasma protein binding; major clearance route (metabolism or renal); rate and extent of skin, liver, plasma metabolism; likelihood of transporter effects etc

Step 6: Supporting a similar MoA hypothesis

6. Data to inform on similar MoA: Untargeted gene expression or protein activity; targeted receptor/enzyme activity or cellular responses etc. Assess weight of evidence to support or refine the biological similarity hypothesis with regards to ADME and MoA. This is likely to be qualitative at this stage, serving to increase confidence in the analogue choice but could include insights into quantitative aspects that can be refined at **Tier 2**.

Analogue(s) with good quality data and hypothesis for RAX – Go to Step 8

Analogues but insufficient data to be confident – Progress to Tier 2

Describe rationale for generating more targeted/quantitative information

Tier 2

Analogues but insufficient data to be confident – End No RAX possible

Step 7: Perform targeted testing to strengthen hypotheses and/or b) Biokinetic refinements of target chemical and analogues

7a. Explain MoA appropriate for the safety assessment based on similarity hypothesis and toxicological relevance. Justify and consider value related to MoA (e.g. Ki/IC_{50}/AC_{10}) in relation to internal exposure (derived in **Step 7b**). Assess relative biological potency of target versus analogue(s) to derive relative potency factors (RPF). Refine as necessary based on in vitro biokinetic considerations (measured or modelled).

AND/OR

7b. Explain internal exposure metric for safety assessment based on mechanistic considerations e.g. C_{max}, AUC; free or total concentration; intra- or extracellular concentration. Build a PBK model for the target and relevant analogues and produce kinetic profiles for analogue (toxicity data) and human use scenarios (defined/refined in **Step 1**) to derive internal exposure values (defined at start of **Step 7b**). Verify model outputs (e.g., using in vivo/human data or PK analogues). Run sensitivity and uncertainty analysis versus established criteria for PBK models.

Perform Next Generation Risk Assessment

Step 8: Perform a RAX to derive a PoD

8. With suitable *in chemico*, toxicology data and NAM data for the analogue(s) from either **Tier 0**, **Tier 1** or **Tier 2** evidence, and with a substantiated hypothesis of similarity between target and source chemicals, the PoD from the most suitable analogue(s) can be used as a basis for deriving a PoD for the target chemical.

Step 9: Perform a MOS evaluation

9. Derive a Margin of Safety (MOS)
Tier 0 MOS ≥100: PoD source / target exposure
Tier 1 MOS ≥100: PoD source / target exposure
→ Can allow for some adjustment using systemic exposure dose and kinetic assumptions e.g. default oral absorption
Tier 2 MoIE ≥25: PoD_{sys} source / ($target\ exposure_{sys}$ X RPF*) *if NAM data allow
→ Assumes that kinetics are fully accounted for which allows the interspecies TK uncertainty factors (UFs) to be set to 1
→ Further adjustment of UFs may be possible using dynamic information

Go to Step 10 to assess confidence in the risk assessment

Step 10: Assess level of confidence for establishing if the MOS is acceptable

10. Describe overall level of confidence (low, medium or high) that the RAX is appropriately conservative as part of an exposure driven risk assessment. If overall confidence is not acceptable e.g. method reliability, data quality and extent of data, what additional information is required to increase confidence or are additional UFs required?

Summary

- This 10-step read-across (RAX) framework is proposed for use in cases where a TTC approach to cosmetics safety assessment is not possible. Two case studies based on this have been published in the OECD IATA project: parabens and caffeine (OECD https://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm)
- RAX builds on established approaches by further substantiating hypotheses on toxicological similarity of substances, and integrating new approach methodologies (NAM) in the biological and kinetic domains.
- This is a robust approach to use RAX in regulatory risk assessment of cosmetics and could be considered for application to chemical assessment beyond cosmetics.

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