Luxembourg, 13 January 2025

Scientific Committee on Consumer Safety (SCCS)
Meeting of the Working Group on Methodologies

10 December 2024, Brussels

Scientific Workshop on Next Generation Risk Assessment (NGRA) for Cosmetic Ingredients
Cosmetic Ingredients

MINUTES

1. Welcome and presentation of the Programme

Head of Unit Health monitoring and cooperation, health networks hosting the Secretariat of the Scientific Committees in Luxembourg, opened the scientific workshop.

The SCCS Vice-Chair and Chair of the SCCS Working Group on methodology welcomed the 60 participants including representatives from SCHEER/SCCS, cosmetic associations & industries, universities, national authorities, EU Agencies and Commission services. She presented the outcome of the SCCS evaluation of a first pilot *Next Generation Risk Assessment* - NGRA dossier on UV-filter Benzophenone-4. She reminded that, **for the SCCS**, **New Approaches Methodologies are animal free-NAMs for cosmetics** due to the ban since 2013.

This was a closed scientific workshop on SCCS invitation only. All speakers presented their work for the purpose of the meeting discussion only, without permission for distribution or publication.

The goal was to discuss a way forward for the SCCS cosmetic ingredients' risk assessment without animal data in the safety file. Some conclusions were drafted for SCCS reflection and internal use (no mandatory commitment) by the Chair of the SCCS.

2. Presentations made

- *EFSA: Criteria for PBPK modelling acceptance for new substances for which no in vivo data are available*

The application of Physiologically Based (Pharmaco)Kinetic (PB(P)K) modelling in the risk assessment of cosmetic ingredients has become increasingly relevant in the context of animal testing bans, particularly for substances where traditional *in vivo* data from repeated dose toxicity or reproductive toxicity studies are unavailable. The presentation explored the necessary criteria for PBK model acceptance in the risk assessment of new substances under these circumstances taking into consideration the OECD 331 PBK model guidance (OECD 2021). By identifying the key criteria for PBK modelling in the absence of extensive *in vivo* data, this presentation was seeking to inform regulatory bodies, industry stakeholders, and scientific researchers on best practices for applying PBK in the NGRA of new substances under the evolving regulatory landscape.

- *Beiersdorf AG: Practical application of in vitro to in vivo extrapolation in cosmetic ingredient risk assessment*

PBPK modelling provides a means for quantitative *in vitro* to *in vivo* extrapolation (QIVIVE), enabling the implementation of NAMs and NGRA in the risk assessment of cosmetic ingredients. In addition, *in vitro* ADME parameters (i.e. Absorption, Distribution, Metabolism, and Excretion) can be integrated in a PBPK model to assess toxicokinetics, and to estimate internal exposure relevant for risk assessment. The tools are broadly applicable for hazard characterization and determining safe exposure levels of cosmetics ingredients using NAM-based Points of Departure (PoDs). As these methodologies continue to evolve, the presentation was explaining that this will play an increasingly central role in regulatory decision-making, enabling a shift toward more protective, human-relevant, and non-animal-based testing frameworks.

- *Joint Research Centre (European Commission, Ispra): Readiness Criteria - Concept, structure and coverage of template proposed by JRC for Guidance 34 revision*

In the context of the OECD GD 34 "*Guidance Document on the validation and international acceptance of new or updated test methods for hazard assessment*" revision, a subgroup was proposed to develop a template that would be included in the OECD GD. The template proposal, developed by the Joint Research Centre (JRC), was based on several background documents and considers only essential criteria that must be fulfilled before a method enters validation, before transferability and before peer-review. The proposed criteria for the phase "*before entering validation*" could be also useful for the purposes of the SCCS, which is to judge the "validity" of non-animal and non-validated methods before they can be used in the actual evaluation process for cosmetic ingredients' risk assessment. The template includes criteria covering important aspects such as test method definition, reliability and relevance. A short reference was also made to the new, currently under development, OECD GD on the Generation, Reporting, and Use of Research Data for Regulatory Assessments, led by the JRC.

- *Belgian federal agency for medicines and health products - Chair of 3R working party EMA: Criteria to accept valid animal-free NAMs for drug development:*

The European regulatory network has a long-standing commitment towards the application of the principles of Replacement, Reduction and Refinement (3Rs). This is driven both by the requirements of Directive 2010/63/EU, as well as by the crucial need for better tools to predict quality, safety and efficacy of new medicinal products. In this context, the leverage and qualification of non-animal approaches is seen as important and requires discussion on and definition of regulatory acceptance criteria (e.g. context of use, endpoints and reference compounds). To this end, the 3Rs Working Party (3RsWP), set up as the official 3Rs hub for at the European Medicines Agency (EMA), initiated a broad set of activities dedicated to fostering the 3Rs in regulatory testing of human as well as veterinary medicinal products. This presentation provided a regulatory view on the specific challenges and opportunities related to the regulatory acceptance of non-animal approaches for the testing of human medicinal products.

- *Beiersdorf AG / International Collaboration on Cosmetics Safety – ICCS / E: Toxicodynamics toolbox in animal-free risk assessment of cosmetic ingredients:*

In compliance with the animal testing ban for cosmetics, the identification of potential mode of action and the corresponding point of departure for systemic toxicity (PoDsys) must be evaluated by appropriate targeted animal-free NAMs (new approach methods). The use of a toxicodynamics toolbox is presented together with suitable assays. A Cheminformatics & In silico Toxicodynamics Tool as part of the toolbox is combined with Toxicogenomics, Cell Stress Panel, Pharmacology Profiling Panel and Functional tests, which could for instance also cover developmental and reproductive toxicity endpoints.
Many case studies with focus on systemic toxicity with NAMs have been undertaken in recent years, especially under the umbrella of the Cosmetics Europe Long Range Science Strategy (LRSS), also including the use of a toxicodynamic toolbox. In this presentation, an example of a read-across (RAX) and an example of an ab initio case study demonstrated the value of the toolbox in the determination of PoDsys.

- *Unilever: Practical use of Bioactivity Exposure Ratio (BER) in animal-free cosmetic ingredient risk assessment*

Bioactivity Exposure Ratio (BER) or Margins of Internal Exposure (MoIE) are terms that are used to describe comparing an *in vitro* PoD with an *in vivo* exposure level to inform safety decision making. This talk covered practical experience of applying BERs for decision making as part of a tiered NGRA approach. Different aspects were discussed, including considerations of biological coverage, and how benchmarking BERs for low and high-risk exposures can bring confidence to the use of BERs. Finally, some examples were shared showing how these decisions can be made for chemicals with different modes of action, and the thresholds that can ensure protectiveness with different combinations of exposure and bioactivity tools and analysis techniques.

- *Research Institute for Fragrance Materials – RIFM: Progress in inhalation TTC*

Thresholds of Toxicological Concern (TTC) are generic human exposure threshold values below which there is negligible risk to human health. Developed for oral exposure, oral TTC values have been determined for three structural classes low, moderate, and high toxicity (Cramer class 1 to 3). This classification and oral TTC values cannot be directly extrapolated for inhalation risk assessment. Therefore, the inhalation TTC (inhalTTC) project aims to define appropriate threshold values for inhalation exposure by harmonizing the dataset for *in vivo* inhalation exposure studies and identifying a suitable chemical classification system based on structural and physico-chemical considerations. The presentation focused on the extensive curated TTC database that was constructed, comprising over 950 high-quality repeated-dose inhalation exposure studies for 508 materials, predominantly from rodents.

- *Procter & Gamble: Progress in Internal TTC*

Currently, the TTC pertains primarily to external exposures. One of the next steps in the continued evolution of TTC is to develop this concept further so that it is representative of internal exposures. This *refinement, termed internal TTC (iTTC),* requires a significant amount of data and computational tools that can be used to convert the chemical specific external dose No Observable Adverse Effect Levels (NOAELs) in the TTC database to an estimated internal exposure for each chemical.
The presentation focused on a project that has been actively focused on developing iTTC values in the rat. Areas for improvement in the bottom-up modeling workflows have been identified and will be the primary focus of the project in early 2025.

- *Organisation for Economic Co-operation and Development – OECD France: OECD guidance on regulatory assessment of quantitative structure–activity relationships (QSAR) modelling:*

Work at the OECD continues to evolve with global trends towards increasing the throughput and decreasing the use animals used in chemical assessments. To that end, new approach methods, including *in silico* models used to predict the potential hazards of chemicals, can support these objectives if models are demonstrated to be reliable and reproducible. The QSAR Toolbox, co-led by OECD and the European Chemicals' Agency (ECHA), is a publicly available software application that was developed for regulatory authorities and other stakeholders to fill gaps in data on chemical hazards. Along with the software, guidance on how to assess the scientific validity of computational models helps regulators build trust in QSARs and other computational methods. Recent work in the Hazard Assessment Programme has focused on how to increase the consistency and transparency of the regulatory review of QSAR predictions. The QSAR Assessment Framework (QAF) was published in 2023 with the aim of helping to establish confidence in the use of QSARs for evaluating chemical safety. Version 2 of the QAF, published in 2024, includes a reporting format for QSAR results derived from multiple predictions. This presentation provided an overview of OECD work on QSARs and the QAF.

3. SCCS Conclusions

- Are NAMs as trustable as *in vivo* methods for regulators? Over the years, there seems to be a move from unlikely to likely for some toxicological endpoints.
- The ban on animal testing in the cosmetic sector brings challenges for new ingredients/product developers as well as regulatory risk assessors -> several key methods are available but a framework for 'which?', 'how many?', and 'what to do?' are still missing.
- A Next Generation Risk Assessment (NGRA) approach could be an alternative to the conventional risk assessment, but it still needs to be aligned for assessors/regulators.
- Scientifically valid vs validated methods /weight of evidence: collective evidence will add credibility and more confidence to risk assessors.
- Quantitative risk assessment of cosmetics is required by legislation – it can not be hazard based alone.
- Questions remain such as:
    - Aligning a NAM with KE(s) in an Adverse Outcome Pathway (AOP) adds a lot of weight in terms of acceptability for regulatory risk assessments but AOPs are not known for most cosmetic ingredients. Can a mode of action be derived from read across?
    - While a systemic harmonised NGRA framework is developed for chemical ingredients, supported by case studies, what about nanomaterials and chemical mixtures used in cosmetics?
    - A number of good proposals were presented at the workshop – e.g. for toxicokinetics/ toxicodynamics, quantitative IVIV extrapolation – internal exposure vs total plasma concentration to parent compounds and metabolites, linking external dose via reverse dosimetry to realistic human exposure. However, the proposed NGRA toolbox offers multiple choices/possibilities (different NAMs, cell types, in silico models, RAx, OMICs) – how to develop it in a way that it is flexible but produces the same outcome when used by different people, or with different choices. Also, how to account for uncertainties when modelled data is used in further modelling/extrapolations?
    - A qualification system for scientifically valid NAMs -> who endorses it?
    - Practical use of *Bioactivity Exposure Ratio* - BER (activity or adversity?) what would be an acceptable threshold for systemic safety of cosmetic ingredients?
    - Exposure based-approaches such as inhalation TTC, internal TTC are under development and therefore not yet ready for practical implementation in human-based risk assessment
    - Standardised assessment of QSARs has been made available, not yet for RAx, but it is in progress.
    - Who takes the lead for further NGRA development?

4. Next steps

The SCCS will discuss all new information received during their next WG meetings on Methodology. Experts may be invited on AD-HOC basis to further discuss some points of interest. For example: (i) to reach consensus on possible criteria for standards to be used for NAMs that are taken up in a risk assessment framework for cosmetic ingredients. (ii) to discuss progress made in animal free risk assessment in the context of 'Developmental And Reproductive Toxicity' (DART).

In that context the audience and in particular representatives from Cosmetics Europe replied positively and wish to continue the dialogue.

As a follow up, the SCCS expressed the idea to write, together with the presenters, a second perspective scientific paper to propose a way forward based on different scientifically valid and validated NAMs that could be used in an *ab initio* NGRA of new cosmetic compounds for which no experimental animal data exists.
