Implementation of an SAR- and analogue-based approach to chemical safety assessment

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Introduction

The increasing ethical and societal demand for reducing animal testing in chemical safety assessment manifested itself regulatory-wise in the recent REACH Regulation (EC) No 1907/2006 and even more so in the amendments of to the Cosmetics Directive 76/768/EEC and its successor legislation, the EU Cosmetics Regulation (EC) No 1223/2009. While REACH mandates that every effort be made to avoid animal testing and that animal testing should only be conducted as a last resort, requires the cosmetics legislation a progressive phasing out of animal tests for the purpose of safety assessment of cosmetics and its ingredients by March 2013. In view of these regulatory demands, the long horizon for the development of fully validated non-animal tests and the limited applicability domains of existing predictive models (e.g., QSARs), "read across" is the most actionable short/mid-term strategy for reducing animal use (Wu *et al*., 2010, Blackburn *et al*., 2011). Existing guidelines that have been developed on toxicological grouping by the OECD (2007) and under REACH (ECHA, 2008) propose a stepwise approach for analogue-based read across to assess chemicals in the presence of data gaps.

Existing regulatory guidance documents do, however, not provide details on the process for judging if identified analogue data are suitable for filling endpoint-specific data gaps. Wu *et al*. (2010) and ECETOC (2012) published frameworks and decision trees considering chemical reactivity and biochemical principles for identifying and justifying analogue data to be suitable for read-across purposes. This poster presents the essential steps and tools necessary to evaluate the suitability and choice of analogue for safety assessment purposes in a transparent and reproducible way. Focusing on publicly available analogue identification and SAR assessment tools, it illustrates on the basis of generic exemplar case studies how, in a formalized and documented approach, analogue data can be used and justified for non-animal based safety assessment of cosmetic ingredients but also to meet regulatory requirements under REACH.

1. Analogue Identification for Chemical of Interest (CoI)

Search strategy based on key structural/sub-structural features, functional groups and metabolic considerations

Tools:
e.g., OECD QSAR tool box, ChemIDPlus, US EPA AIM, Toxmatch, proprietary databases, literature search and expert judgment

2. Analogue/CoI Similarity Analysis

2a. Chemical structure & reactivity

Features to be evaluated include commonality of structural alerts and functional groups, position of double bonds and additional reactive groups;

Tools:
e.g., OECD Tool Box, US EPA Aim, Chemmine, DEREK™, literature search and expert judgment.

2b. Metabolic pathways

Features to be evaluated relate to potential of analogue to metabolize to target (or vice versa), formation of common stable or reactive metabolites with same MoA or bio-activation pathways leading to different toxicological profile

Tools:
e.g., MetaPrint 2D, OECD Tool Box, Meteor™, literature search and expert judgment.

2c. Physicochemical properties

Properties to be focused on are those that are presumed to impact the bioavailability and metabolic fate of the CoI/Analogue, i.e., molecular weight, partition coefficient (logKow), water solubility or ionization constants (pKa).

Tools:
e.g., Episuite, ChemSpider, ACD™ and literature search

3. Analogue Suitability Rating
(according to Wu *et al*., 2010)

Suitable
Analogue is nearly identical on all 3 suitability parameter

OR

Suitable with interpretation
Analogue and CoI have the most salient features in common; differences typically relate to PC parameter impacting bioavailability

OR

Suitable with precondition
Analogues are suitable to be used for CoI assessment assuming a particular condition such as a hydrolytic or metabolic process is met (often in vitro confirmation required)

OR

Not suitable

4. Toxicological Review and Analogue-based CoI Assessment

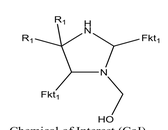
Depending on level of confidence, required toxicological endpoint is assessed on the basis of analogue data followed by identification of a NOAEL required for safety assessment purposes

Case study I: Analogue-based safety assessment of a substitute imidazolidine derivative

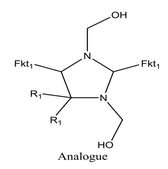
Example: To allow the toxicological assessment of a data poor substituted imidazoline derivate, a number of structurally similar substances were identified based on structural features ('imidazolidine'), substitutes ('R1') and key functional groups ('Fkt1') using the OECD toolbox as well as expert search in proprietary databases. A number of analogues were suggested by the tools out of which 2 analogues were considered suitable ('Analogue 1') or suitable with interpretation ('Analogue 2'). Sufficient toxicological information was only available on 'Analogue 2' which is called in the following 'Analogue'.

Key data/information for CoI and Analogue

- Chemical similarity of CoI and Analogue (i.e., Tanimoto score ≥ 0.75)
- Similar physico-chemical properties and structural alerts for CoI and Analogue in SAR tools like the OECD tool box and DEREK™;
- Predictive tools as well as expert judgement predicted common metabolic paths and metabolites for CoI and Analogue;
- Comparable low acute toxicity profile of CoI and Analogue (*in vivo* data);
- Analogue was a sensitizer in an LLNA as well as in and HRIPT;
- Analogue has been evaluated in an oral 90d toxicity study with no toxicological significant effects at highest dose of 250 mg/kg/day;
- Predicted absence of genotoxicity and overall low toxicity of Analogue as well as absence of structural alerts for carcinogenicity suggests that the CoI is unlikely to represent a carcinogenicity hazard;
- No DART data exist on CoI; with Analogue, neither effects were observed on the reproductive system nor developmental toxicity in an OECD TG 414 study were observed.



Chemical of Interest (CoI)



Analogue

Conclusion: Following the structured process of establishing chemical , reactive and metabolic similarity, it is concluded that the chemical of interest can be assessed based on the data available for Analogue. The latter is expected to exert a higher toxicity due to its potential to release of 2 equivalents of formaldehyde. Of critical consideration for cosmetic applications is the likely skin sensitisation potential of the CoI. An appropriate 'NESIL' (No Expected Sensitization Induction Level) can be derived on the basis of available data on Analogue .

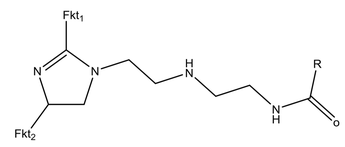
Case study II: Use of SAR/Analogue assessment framework to support category justification under REACH

Example: For the purpose of a REACH registration, a chemical category of UVCB substances was established. As a result of varying process conditions, the individual category members mainly differed in their relative content of 4 main constituents (with characteristic substructures). One category member contained a low level of a 5th constituent (CoI) and the question was raised whether this substance could be assessed on the basis of the toxicological data available on the other category members ('Analogue'). For simplicity reason, the case is discussed by comparing the generic structure of the analogue's main constituent considered to determine its toxicity in comparison to that of the CoI.

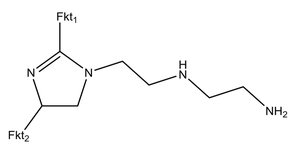
Key data/information for CoI and Analogue

- Chemical similarity of CoI and Analogue (i.e., Tanimoto score ≥ 0.75);
- Incremental and constant change of physicochemical characteristics of category members as a result of increasing chain length and molecular weight (measured);
- No differences in key functional groups and structural alerts as identified by the OECD tool box across

  the different category members (Note: below structures of CoI and Analogue indicate an additional amide-group in the 'Analogue'; this functional group is present in two other substructures, hence no difference);
- Under physiological and metabolic conditions, the Amide group in the CoI is expected to readily hydrolyse to the 'Analogue' (i.e., the free amine)



Substituted Imidazoline Amide (CoI)



Substituted Imidazoline Amine ('Analogue')

Conclusion: The toxicological activity of the CoI is assessed to be very similar to that of the 'Analogue', leading to the assessment that the additional 5th constituent does not alter the toxicity of the respective category member. It can therefore be assessed on the basis of toxicology data available on the other category members by means of read-across.

References

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