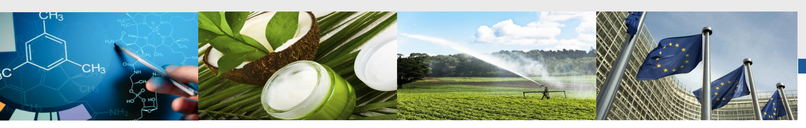
An integrated SAR-and Analogue-based approach to Chemical Safety Assessment

T. Petry, M. Autiero, D. Jeronimo-Roque and F. Tencalla

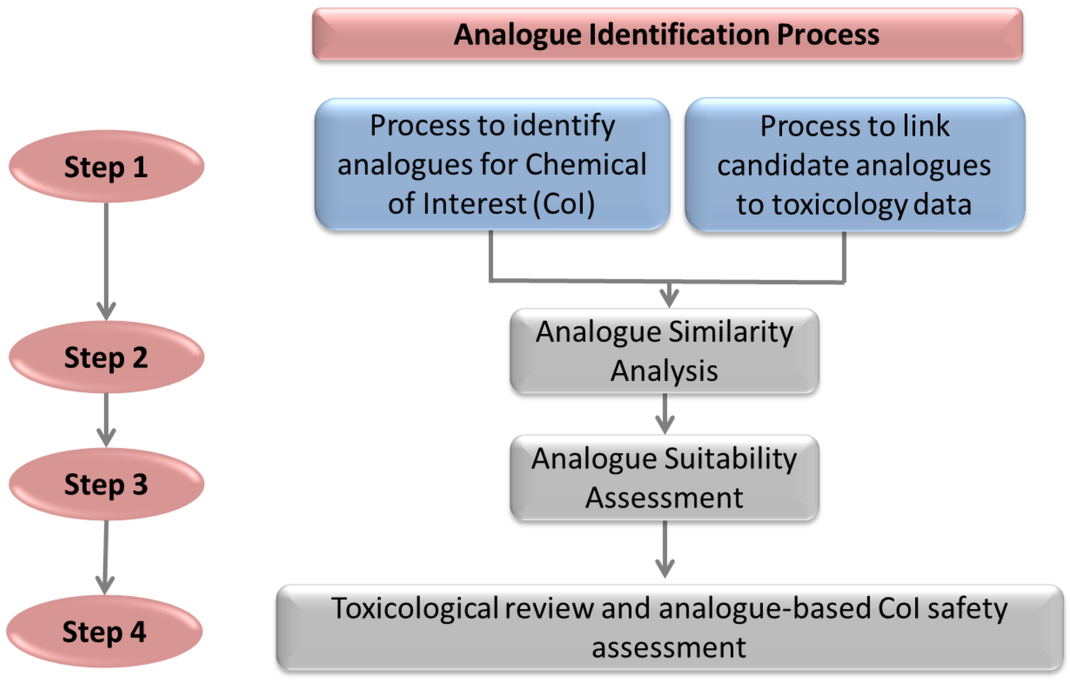
ToxMinds BVBA, Avenue de Broqueville 116, B-1200 Brussels, www.toxminds.com



Introduction

In response to the increased ethical and societal demand for the reduction and phasing out of animal testing for hazard assessment purpose, a substantial amount of publicly or privately funded research initiatives were launched, all with the aim to improve our ability to predict the biological effects of chemical compounds on the basis of their molecular structure and physico-chemical (PC) characteristics. As a result, a huge number of IT-tools and databases have been developed that support the toxicologists in predicting the toxicity of the chemical of interest (CoI) on the basis of structure activity and analogue data. Substantial experience is required to evaluate the suitability of SAR-/analogue-based hazard assessment approaches. It is further crucial that a transparent and criteria-based process is in place documenting all steps, data and considerations leading to the final suitability justification. This poster presents an integrated approach which we thoroughly checked against publicly available data and case studies, allowing the selection of suitable analogues for assessment for any toxicological endpoint. It is based on the use of publicly available IT tools and data bases paired with expert judgement to evaluate the similarity between the CoI and analogues with regard to chemical structures and reactivity, metabolic pathways and physico-chemical/toxicokinetic properties. Overall, this stepwise approach allows the identification and ranking of analogues to be used for hazard assessment in a reproducible and transparent manner including a description of related uncertainties. It is suitable for use in context of establishing business strategies, regulatory submissions (e.g., REACH, BPR, Food Contact) or in a general product safety and stewardship context.

SAR-/analogue-based safety assessment process: The picture



Step 1: Analogue Identification Process

Tools to identify analogues

- Searchable databases (by similarity, structure and substructure)
- Routinely – publicly available: e.g., OECD tool box, US EPA AIM, ChemMine, EPA DSSTOX
- Occasionally – proprietary databases, literature and expert judgment

Profiling criteria

- Set experience-based threshold (e.g., tool box), fragment and similarity criteria (AIM) or cut-offs in the respective tools
- Vary criteria depending on number of analogues identified (respect lower experience-based thresholds!)
- Sub-categorize analogues by using critical structural alerts (e.g., DNA/protein binding, genotoxicity)

Link to toxicology data

- OECD tool box and AIM provide some indication of data availability; additional literature screening for prioritized analogues required (e.g., ECHA, ToxNet, eChemportal)

Step 2: In-depth Analogue Similarity Analysis

Chemical structure and reactivity factors

- Common structural alerts associated with known toxicity *(e.g., aromatic/secondary/hydroxyl amines, epoxides, quinones, α,β unsaturated aldehydes)*
- Common functional groups & core structures *(e.g., ester, aldehyde, amide, amine, alkyl chains, phenyl ring)*
- Position of double bonds *(particularly conjugation or relation to functional groups)*
- Effects of additional functional groups

  Tools: e.g. OECD tool box, AIM, ChemMine, ChemIDPlus, proprietary DB (e.g., Derek™)

Physico-chemical and toxicokinetic evaluation

- Molecular weight; measured or predicted values for PC endpoints: melting/boiling point, vapour pressure, Kow, water solubility dissociation constant (pK_A, pK_B)
- In *vitro*/*vivo* or modelled information on dermal, pulmonary or gastrointestinal absorption of COI and analogues

  Tools: e.g. EPI Suite, ChemSpider, OECD tool box, desktop/literature search, proprietary DB (e.g., ACD™)

Metabolic pathway assessment

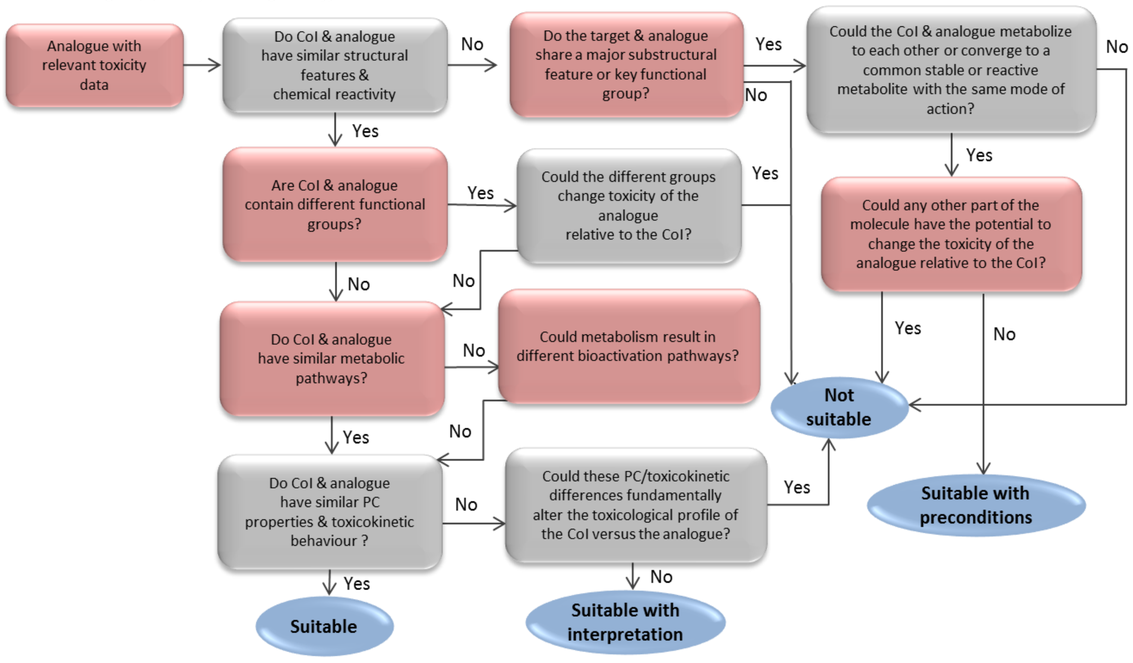
- CoI and analogue are structurally similar
  - *Is there potential for CoI and analogue to have different metabolic pathways?*
  - *Do CoI and analogue produce metabolites of different toxicities?*
- CoI and analogue are not structurally similar
  - *Are CoI and analogues metabolites of each other?*
  - *Are they expected to converge to a similar metabolite?*
  - *Are they expected to produce metabolites of different toxicities?*
- Documentation of metabolism assessment
  - *Predicted metabolism pathway as far as possible*
  - *Justification for assumption of similar toxicity related to metabolism*

  Tools: e.g. OECD tool box, MetaPrint2D, SMARTCyp, proprietary DAB (e.g., Meteor™, Accelrys™); Weight-of-Evidence analysis and expert judgment

Step 3: Analogue Suitability Assessment

Analogue categorization *(adjusted from Wu et al., 2010)*

- Suitable - *Analogue is nearly identical to the CoI on all parameters*
- Suitable with interpretation – *Analogue(s) contain most salient CoI structural features and key functional groups; it may contain additional groups which lead to differences in e.g. PC properties and/or metabolic pathways, but no major different toxicities are expected*
- Suitable with precondition – *CoI and analogue(s) are metabolites of each other (e.g., ester/amide bond hydrolysis products); metabolism is required for CoI and analogue(s) to converge to same structures; depending on level of uncertainty, additional in vitro data may be required to support the assessment*
- Not suitable – *Differences in structure, functional groups, PC/TK properties and/or divergent metabolism between COI and analogue(s) likely leading to differences in toxicities*



Output and documentation

- Excel matrix containing for CoI and each Analogue
  - Chemical identifiers (CAS#, EINECS#), structures and smiles codes
  - SAR evaluation (chemical structure & reactivity factors)
  - PC , toxicokinetic and metabolism evaluation
  - Available or modelled PC, (eco)toxicology and environmental data
- Analogue suitability assessment

Step 4: SAR-/Analogue-based Chemical Safety Assessment

Standard process to hazard assessment

- Comprehensive desktop search for relevant toxicological information
- Data quality review and compilation of suitable studies on CoI and suitable analogues for each endpoint into CoI/Analogue data matrix
- WoE analysis and derivation of safe exposure levels under consideration of underlying uncertainties (see below)
- Completion of hazard assessment according to specific regulatory requirements (e.g., REACH, Cosmetics - PIF, food contact materials) or for general product safety stewardship purposes

Important Considerations

Issue: Uncertainties

- Outcome of an SAR-/Analogue-based chemical assessment still depends to some extend on the quality of the underlying databases and the experience of the risk assessor
- Lack of consistency – disagreements between risk assessors in less obvious cases
- Lack of transparency in how conclusions were derived

Aspects to consider in uncertainty analysis (*see also Blackburn K. and Stuard S. (2014)*)

- Number of analogues contributing data
- Robustness of analogue data set
- Concordance of effects & potency across analogues and CoI anchor data
- Severity of critical effect

Summary

SAR-/analogue-based chemical safety assessments require

- A ***transparent process*** integrating the key aspects
  - chemical similarity and reactivity, structure activity and known toxicity
  - physico-chemical properties
  - metabolic pathways and toxicokinetic behaviour
- ***Reproducible documentation*** including the read-across hypothesis, data underlying the analogue suitability and WoE hazard assessment as well as a discussion of uncertainties

References

Wu S. *et al*., 2010. A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogues for SAR-based toxicological assessments. Regulatory Toxicology and Pharmacology 56, 67-81.
Blackburn K. and Stuard S., 2014. A framework to facilitate consistent characterization of read across uncertainty. Regulatory Toxicology and Pharmacology 68, 353-362.