Development of Integrated *In Silico* Models for Toxicity Prediction Focussing on Cosmetic Ingredients

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Introduction and Aims

Computational approaches play an important role in the toxicity prediction of chemical substances and their role in risk/safety assessment is anticipated to further increase. However, the modelling of repeated dose toxicity remains a challenge due to the lack of available toxicological data and the complexity of the chemical and biological interactions leading to the adverse effects caused by long-term low-dose exposure to a substance. Furthermore, methods are needed to predict target organ concentrations, accumulation of chemicals and their metabolites, and to extrapolate from *in vitro* to *in vivo* organ level dose. To solve these challenges and to contribute to the safety assessment in particular of cosmetic ingredients, the 15 partner COSMOS Project is developing synergistic workflows integrating different approaches for toxicity prediction.

Existing Data

- **Creation of a database** with different access levels to capture repeated dose toxicity as well as dermal absorption and metabolism data
- **Data quality assessment and quality control**, both of chemical structures and toxicity data
- **Comprehensive COSMOS inventory of cosmetic ingredients** with currently over 5500 well-defined, unique chemical structures

Grouping Similar Chemicals

- **Formation of categories of similar compounds using reactive fragments, associated with known mechanisms of toxicity**
- **Mechanism-based profilers developed and coded as SMARTS and CSRLM language patterns to define chemotypes, allowing the grouping of similar compounds and searching of sets of data; implemented as a KNIME workflow**
- **Data available for the compounds in the category, e.g. from the COSMOS database, may be used for read-across to predict missing toxicological data**

Modelling of Biokinetics

- **Consideration of toxicokinetics and toxicodynamics** and better understanding of the effect of the test system properties (e.g. sorption) and chemicals (e.g. volatility, stability) for extrapolation from *in vitro* to *in vivo* target organ level dose (*IVIVE*)
- **Process-based models** predicting relevant concentrations and dynamic behaviour in cell-based assays
- **Prediction and modelling of the absorption, distribution, metabolism and excretion (ADME) properties to build physiologically-based pharmacokinetic (PBPK) models**
  - **Multi-scaling modelling approach integrating cellular and organ models for predicting spatiotemporal variations in toxicity**

Safety to Humans of Cosmetic Ingredients

**In Silico Approaches**

- **Innovative toxicity prediction strategies based on chemical categories, read-across and (Q)SARs should be related to key events in Adverse Outcome Pathways (AOPs).**
  - **In silico modelling supports a number of activities:**
    - (Q)SAR modelling of skin penetration, oral absorption, metabolism (skin vs liver)
    - Grouping driven by AOPs: fibrosis (chemotypes and alerts), steatosis (3-D receptor modelling)

Exposure

- **Exposure considerations important for risk assessment, e.g. formulation, concentration and route of exposure to cosmetic ingredients**

Bioavailability and Metabolism

- **Differences oral and dermal exposure:**
  - Absorption/permeability via dermal or oral routes
  - Metabolism: detoxifying or toxifying effect, new compounds created
  - Metabolism differences between skin and liver

Modular Integrating Platform

- **Integration of the access to databases and modelling approaches into flexible computational workflows**
- **The KNIME* technology allows for the creation of such adaptable workflows and provides a useful and versatile tool assisting in the prediction of human repeated dose toxicity and the safety assessment of cosmetic ingredients**

Conclusions

- **Computational modelling, including biokinetic approaches, supports toxicology and risk assessment in a number of key areas**
- **Mechanistic information needs to be integrated through AOPs**
- **COSMOS is at the heart of efforts to integrate different modelling approaches and chemoinformatics methods for in silico toxicity predictions to support the safety evaluation for cosmetic ingredients and beyond**