COSMOS – Computational Models for Determining the Safety of Cosmetic Ingredients to Humans

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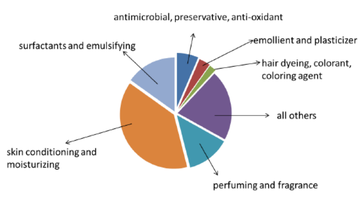
COSMOS is developing methods to predict the effects of long-term exposure to cosmetic ingredients and determining the safety for humans, without the use of animals, using computational models

Existing Data

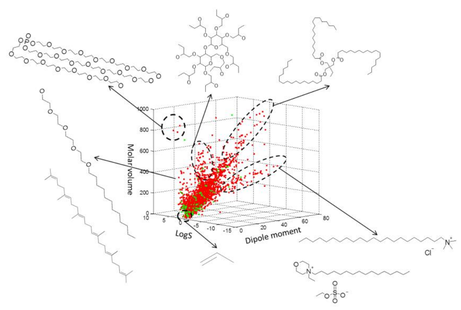
- **Database framework** with different access levels capturing repeated dose toxicity as well as dermal absorption and metabolism data
- **Data quality assessment and quality control**, both of chemical structures and toxicity data



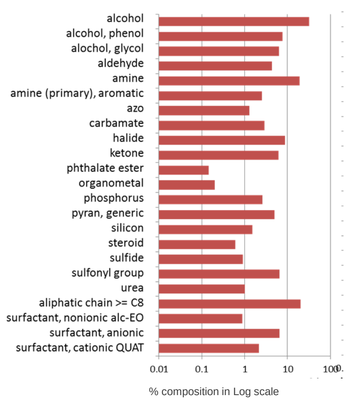
- Comprehensive **COSMOS inventory of cosmetic ingredients** and related substances with over 4400 well-defined, unique chemical structures

Chemical Space

- Representation of the **structural features and/or molecular properties** covered by a defined set of chemicals
- Assessment of the COSMOS inventory/dataset for its representation of the chemical space of cosmetic ingredients, by analysing structure and physico-chemical property descriptors



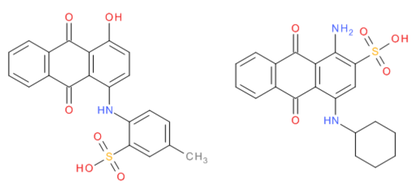
Physico-chemical space of the COSMOS Cosmetics Inventory and TTC dataset.



Structural classes in the COSMOS Cosmetics Inventory.

Grouping Similar Chemicals

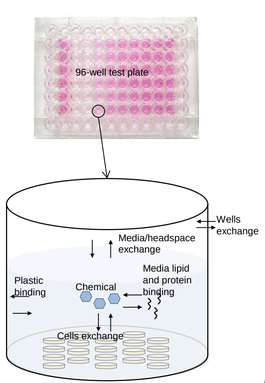
- **Formation of categories of similar compounds** using fragments associated with known mechanisms of toxicity



- Development of **mechanism-based profilers** and coding as SMARTS* patterns to define chemotypes, allowing the grouping of similar compounds and searching of sets of data * http://www.daylight.com
- 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

Biokinetics Modelling

- 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) required for extrapolation from *in vitro* to *in vivo* organ level dose (**IVIVE)**
- Process-based model for prediction of relevant concentrations and dynamic behaviour in cell-based assays
- Prediction and modelling of the absorption, distribution, metabolism and excretion (**ADME**) properties of a compound



Safety to Humans of Cosmetic Ingredients

In Silico Approaches

- Innovative toxicity prediction strategies based on chemical categories, read-across and (quantitative) structure-activity relationships ((Q)SARs), related to key events in **Adverse Outcome Pathways** (AOPs)
- Synergistic workflows for the prediction of repeated dose toxicity to humans for cosmetics required to **mimic the complexity** of chronic toxicity, involving a complex series of biological effects

Exposure

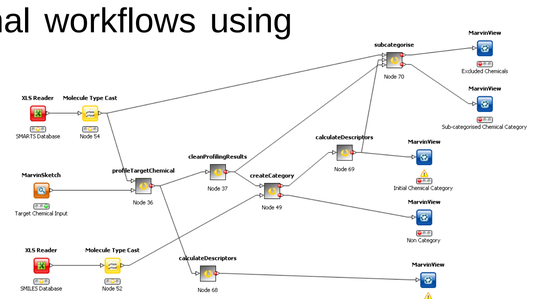
- Exposure considerations important for risk assessment, e.g. formulation, concentration, route of exposure (dermal vs oral) to a cosmetic ingredient

Safe Thresholds

- Exposure threshold for chemicals, below which there is a low probability of an appreciable risk to humans: Threshold of Toxicological Concern (TTC)
- Assessment of the extension of the current TTC approach to cosmetic ingredients and oral to dermal extrapolation
- New non-cancer **COSMOS TTC dataset**, enriched with cosmetic ingredients and more suitable toxicity data, to assist TTC development

Modular Integrating Platform

- Integration of the access to databases and modelling approaches into flexible computational workflows using the KNIME technology
- Example of KNIME workflow for category formation, searching an inventory or a database and retrieving toxicity data:



Conclusions

- Computational modelling, including *in silico* and biokinetic approaches, supports toxicology and risk assessment in a number of key areas
- Mechanistic information needs to be integrated
- Open and flexible platforms to capture modelling processes are required to ultimately support data capture, storage and retrieval, links of chemistry to pathways through AOPs as well as open and transparent modelling to evaluate the safety of chemicals to humans

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