There are currently no validated animal-free replacement methods to assess repeated dose toxicity. This poses serious problems for developing new chemical compounds across various sectors, mainly in the cosmetic industry, where animal testing is fully banned in the EU. However, since biological responses in an animal cannot be reflected using single non-animal methods, it is necessary to use Integrated Approaches to Testing and Assessment (IATA) that rely on an integrated analysis of existing information coupled with the generation of new information using non-testing (e.g. grouping and read-across) and testing methods (e.g. in vitro). The appraisal of all existing information in an iterative approach is considered a core pillar in the search for animal-free risk assessment of chemicals.

Aims

This study aimed at developing a user-friendly knowledgebase (KB) using semantic technology in which existing toxicological data of cosmetic ingredients retrieved from SCCS opinions is gathered and maintained to assist non-animal systemic toxicity assessment. To add more weight to the toxicological evidence, Structural-Activity Relationship (SAR) data supported through the OECD QSAR Toolbox has been implemented in the KB. The use of the KB as hazard identifier tool and guidance for further in vitro testing is showcased in the field of hepatotoxicity.

Results

In silico prediction for hepatotoxicity: weight-of-evidence assessment (objectives 2 & 3)

- HESS (Hazard Evaluation Support System): 9 out of 30 ingredients carrying hepatotoxic structural alert identified by OECD QSAR Toolbox
- VEGA (IRFMN model): 2 out of 30 toxic predictions
- HCV Yellow list is identified as hepatotoxic with both in silico tools
- With both algorithms, the majority of compounds can’t be categorized

Generating additional AOP-based mechanistic in vitro data for liver steatosis

- Basic Red S1 (BR51) tested at sub-cytotoxic concentrations in vitro on human skin stem cell-derived hepatocyte-like cell (hSKP-HPC)
- Fluorescenting of fatty acid with Bodipy after 24h shows an accumulation of fat
- The results of RT-qPCR after 24h exposure suggest this effect is probably due to a downregulation of the expression of APOB
- The expression of other key genes involved in lipid metabolism has significantly been modified such as PPAR

Conclusion

- We developed a tool (TOXIN) based on semantic technology that facilitates data extraction from SCCS opinions.
- Using TOXIN, we retrieved 30 cosmetic ingredients with potential hepatotoxic effects in laboratory animals.
- Integration of OECD QSAR Toolbox in TOXIN improves the weight of evidence regarding hepatotoxicity. To confirm the in silico predictions of the OECD Toolbox, we used the VEGA platform.
- Based on the results of the tool and in the context of NGRA, we further evaluated BR51 in vitro using human stem cell-derived hepatocyte-like cells. We found indications that this compound also induced the accumulation of intracellular lipid suggesting steatogenic potential.