CONTRIBUTION MAPPING: USING STRUCTURE–TOXICITY RELATIONSHIPS (STR) AND MECHANISTIC INTERPRETABILITY OF IN SILICO MODELS TO ASSESS DEVELOPMENTAL TOXICITY AND ENDOCRINE-DISRUPTING POTENTIAL OF TWELVE UV FILTERS
ABSTRACT #220

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In the last years, the safety of some UV filters has been questioned about association with percutaneous permeation into the circulatory system that could lead to hormone diseases. Recently European Commission has opened a call to provide information on endocrine-disrupting (ED) potential of some cosmetic ingredients, aiming a higher level of protection from hazardous chemicals. Predicting ED of compounds is a complex task and should consider 14 different human nuclear receptors that regulate reproduction, behavior, development, metabolism and immune system. One of the challenges on the safety assessment is to develop predictive and unambiguous approaches with mechanistic interpretability. In silico methods have been proposed as key components of a future testing paradigm, providing mechanistic domains for both tested and non-tested molecules. This study aimed to assess the ED potential of twelve UV filters, identifying compounds potentially active (binders, agonists, and antagonists) to in vitro estrogen receptors (ER) and in vivo developmental toxicity. Ingredients were assessed by the tool DevTox-iS, using five Quantitative structure-toxicity relationship (QSTR) models developed to identify potentially active binders, agonists, and antagonists to in vitro ER and in vivo toxicants for the development of mammals. For each model, we explored the contribution mapping with Structure–Toxicity relationships (STR), trying to check fragments that could decrease toxicity/activity (-) (red) or increase toxicity/activity (+) (green), resulting in hypotheses and mechanistic interpretations (OECD Principle 5). Considering the animal testing ban under the Cosmetic Regulation, this study allowed to integrate QSAR docking and computational system biology tools to predict suspects of ED activity as an approach for evaluation to cosmetic ingredients. Integrated in silico strategy with STR mapping can drive the safety assessment, not only eliminating potentially toxic ingredients, but providing mechanistically targeted results for weight of evidence (WoE) of experimental data and predictions in the safety assessment of cosmetic ingredients.

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Physiological map to study kidney toxicity in the ONTOX project
ABSTRACT #428

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Background and Objectives Continuous improvements of computational approaches also increase the predictive performances of toxicological in silico models [1]. However, being mainly based on animal test data, these computational models lack a good correlation with human toxicity, and, being often based uniquely on chemical structures, they are unable to explain toxicological processes. To overcome these limitations, we have developed a new semi-automated strategy to build a Physiological Map (PM), a framework to study human toxicological mechanisms. Materials and Methods Our method is useful to build a PM or to validate an existing PM. To retrieve information, a manual literature review was accompanied by computational interrogation of ontologies (e.g. Gene Ontology), thus creating a network of genes, proteins, molecules and phenotypes [2]. The network was converted

manually into a PM using the CellDesigner software and visualized on the web using the MINERVA platform. The entire procedure was supported and revised by field experts. Results We present here the human kidney PM, developed in the framework of ONTOX, a European project aimed at improving risk assessment avoiding the use of animal tests [3]. With the purpose to better understand tubular necrosis and nephrolithiasis, the PM represents the normal physiology in proximal tubule, the loop of Henle, distal tubule, and collecting duct cells, displaying the vitamin D metabolism and the urine production processes: filtration, reabsorption and secretion. Discussion and Conclusions Our method assists the user to build a PM even starting from limited data. The PM is initially a static representation of physiological processes, also useful to study and develop new adverse outcome pathways. Subsequently, we could add kinetic parameters, transforming the PM into a dynamic model able to represent cellular perturbations. This approach presents an opportunity to investigate human toxicities, improving the toxicological predictions from a qualitative and quantitative perspective.

References

[1] Manganelli S, Gamba A, Colombo E, Benfenati E (2022) 'Using VEGAHUB Within a Weight-of-Evidence Strategy'. In: Benfenati E. (eds) In Silico Methods for Predicting Drug Toxicity. Methods in Molecular Biology, vol 2425. Humana, New York, NY. https://doi.org/10.1007/978-1-0716-1960-5_18
[2] Gamba A, Salmona M, Bazzoni G (2020) 'Quantitative analysis of proteins which are members of the same protein complex but cause locus heterogeneity in disease', Sci Rep 10, 10423. https://doi.org/10.1038/s41598-020-66836-7 [3] Vinken M., et al. (2021) 'Safer chemicals using less animals: kick-off of the European ONTOX project', Toxicology 458, 152846.
https://doi.org/10.1016/j.tox.2021.152846

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QUANTITATIVE ADVERSE OUTCOME PATHWAY MODELING FOR CHRONIC TOXICITY
ABSTRACT #255

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Background and objectives Quantitative adverse outcome pathway (qAOP) – a mathematical representation of an AOP — can be used for risk assessment. Problematically, only a limited number of qAOPs are devoted to chronic toxicity. To address this gap, we developed a hypothetical qAOP for chronic toxicity using Bayesian network (BN) formalism. Our method is flexible, can be used to estimate probability of an adverse outcome and can be generalized to other scenarios. Methods We built a hypothetical AOP with four acute phase MIE and KEs, five chronic phase KEs, and an AO (biomarkers). Accounting for inter-donor difference in primary cells, we generated a primary dataset of each biomarker for a total of eight donors, multiple exposure repetition and dosing. We resampled the primary dataset to build a replicate level virtual dataset. The virtual dataset was then subjected to a dynamic BN modeling for the quantitative risk assessment. We further explored data-driven AOP restructuring using lasso regularization. Results Using our model, we estimated probability of AO based on activation of upstream events at a previous exposure. We found that the strength of interaction changed over time, especially between acute and chronic phase KEs. Our analysis further revealed that some acute-phase KEs were not predictive of AO, suggesting that our model was able to capture when the response transitioned from an acute to a chronic phase. Discussion and conclusion In sum, we developed a BN-based qAOP framework that can be used for risk assessment. Although we used virtual dataset, we believe that this methodology can be applied directly to real data including data from in vitro NAMs. Our results show that cumulative effects from repeated exposures are important and structure of an AOP is dynamic. This formalism can be used retrospectively to gain mechanistic insight.

References

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