A Safe & Sustainable by Design R&D pipeline using *in silico* methodology

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Introduction

To incorporate environmental and human health protection considerations into their Research & Development (R&D) pipeline, companies are moving increasingly toward New Approach Methodologies (NAM). In their desire to reach Safe & Sustainable by Design (SSbD) products, *in silico* methods (e.g. (quantitative) structure activity relationship models, SARs or QSARs) are starting to be integrated into R&D pipelines at an early stage. Such approaches have several advantages: they follow the 3R paradigm (replace, reduce, refine), they are relatively fast and low-cost compared to traditional *in vivo* or i*n vitro* testing and can be used to compare the properties of a large quantity of chemicals simultaneously.

In this context, Chevron Phillips Chemical (CPChem) used an *in silico* method to screen chemicals for a new application. Having selected a substantial number of chemicals that had certain physico-chemical properties, their aim was to help their R&D team reduce the list to just a small number of safer compounds that could potentially be used for a new application. To accomplish this, they requested KREATiS to assess the toxicological effects of a wide range of chemicals using *in silico* methods. Due to both technical and economical considerations, the targeted endpoints for these chemicals were limited to predictions of carcinogenic, mutagenic and reprotoxic (CMR) and skin sensitisation potential using available (Q)SAR tools.

In Silico Tools and Expert Review in Traditional R&D Pipelines improve Successful Identification and Transition to Safe & Sustainable Chemistry

Methods

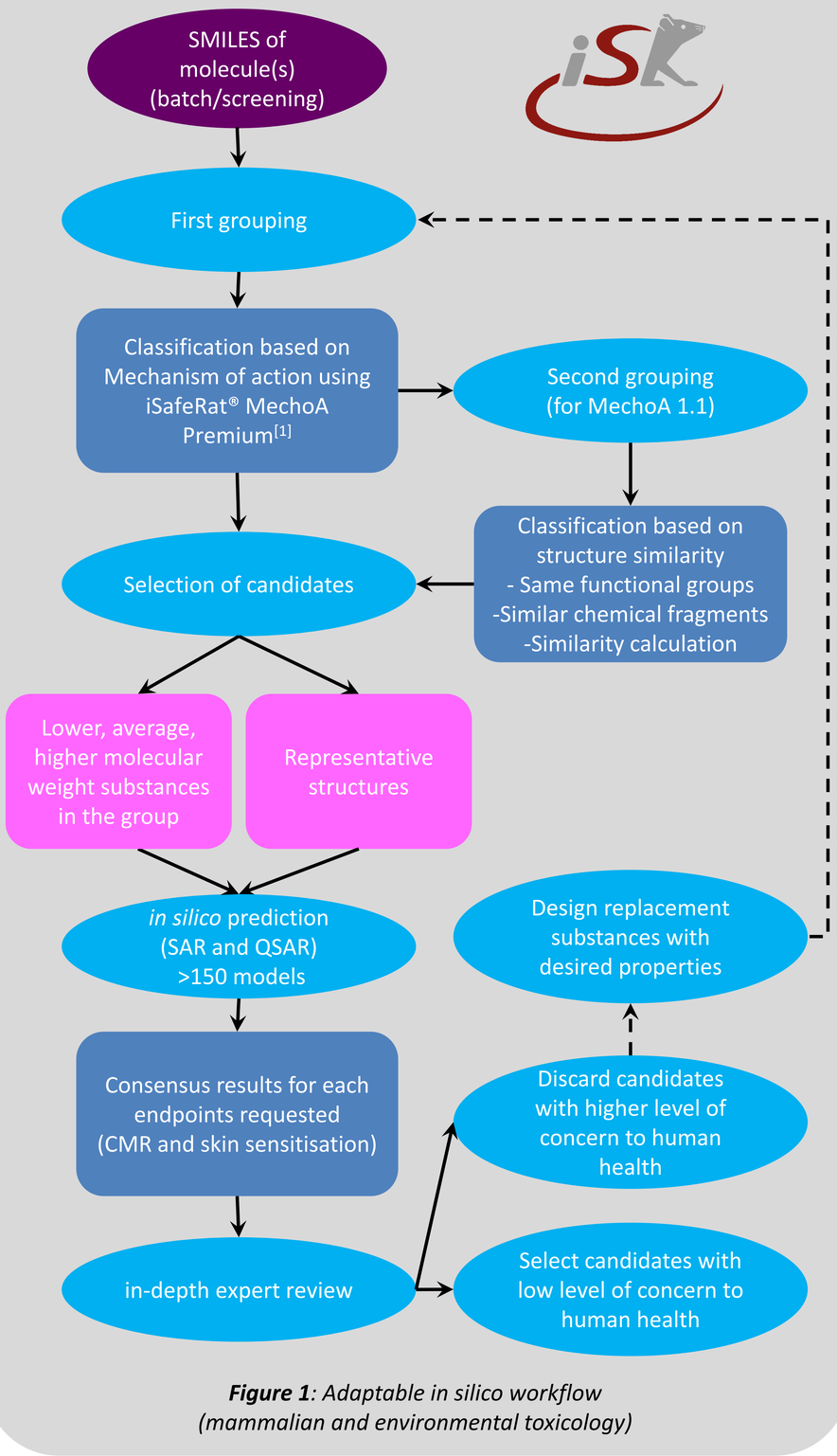
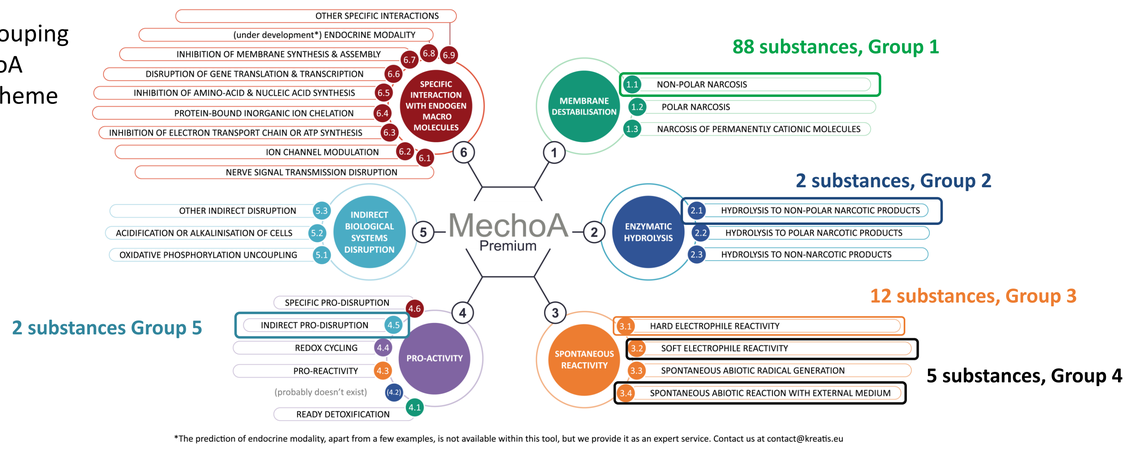


***Figure 1**: Adaptable in silico workflow (mammalian and environmental toxicology)*

Case study

CPChem requested *in silico* toxicology assessment for an initial batch of 110 substances previously estimated to meet the physico-chemical requirements for successful use downstream. To reduce the number of tested chemicals, they were grouped based on mechanism of toxic action (MechoA)[1,2,3] (Figure 2). For substances classified MechoA 1.1 (narcosis), further grouping was needed based on structural insight (Table 1). Representative candidates were then selected from each group (Table 2). Targeted endpoints were evaluated for each candidate using available *in silico* tools (iSafeRat®, VEGA, OECD QSAR Toolbox, OPERA, T.E.S.T, Danish QSAR, DEREK). After expert review of the (Q)SARs results (Table 3), consensus results for each candidate and comments on the groups represented by these candidates were provided. A consensus conclusion for each endpoint is given with a level of likelihood (certainly, probably, plausibly, inconclusive) based only on the reliable predictions obtained for the same endpoint. When no results were judged valid for an endpoint by the *in silico* expert, no consensus was obtained (inconclusive results).

Figure 2: First grouping using MechoA classification scheme



*The prediction of endocrine modality, apart from a few examples, is not available within this tool, but we provide it as an expert service. Contact us at contact@kreatis.eu

Table 1: Second grouping for MechoA 1.1 substances (7 groups formed)

Common structural features	Number of substances in group	Group number
alkene or alkyne	50	1a
ketone (and alkene)	6	1b
alcohol and alkene	3	1c
allylic and propargylic ethers (i.e. ether and alkene or alkyne at a distance of 2 carbons)	18	1d
ethers, non allylic or propargylic (it can contain alkene or alkyne, but not at a distance of 1 or 2 carbons)	6	1e
ether and alkene/alkyne which have the unsaturation in alpha of the ether	4	1f
allene	1	1g

Table 2: Selection of candidates

Group number	Number of candidates	Selection of candidates for toxicological *in silico* screening
1a	4	Lower, average and higher MW representatives + 1 having conjugated groups representative
1b	1	1 aliphatic ketone, 1 ketone-alkene representatives
1c	2	1 cyclic, 1 aliphatic representatives
1d	3	Lower, average and higher MW representatives
1e	2	Lower and higher MW representatives
1f	2	1 ether-alkene, 1 ether-alkyne representatives
1g	1	Only representative
2	1	1 representative randomly chosen
3	2	Lower and higher MW representatives
4	3	1 ester (unique representative), 1 ketone-alkyne, 1 ketone-alkene
5	1	1 ester representative

***Table 3:** Consensus results Group 1a*

Group	1a
Mechanism of Toxic Action	MechoA 1.1: Non-polar narcosis for all species.
Acute oral toxicity	GHS Cat. 5 (probably)
Protein binding and skin sensitisation	Non-sensitiser (certainly)
DNA binding, Mutagenicity and Genotoxicity	Inconclusive
Genotoxicity *in vitro* (bacteria)	Non-mutagenic (certainly)
Genotoxicity *in vitro* (mammalian cells)	Inconclusive
Genotoxicity *in vivo* (mammalian)	Genotoxic (probably)
Developmental and Reproductive Toxicity (DART)	Non-toxicant (plausibly)
Carcinogenicity	Non-carcinogenic (certainly)
Additional comments	*(additional information are confidential and not provided)*

Discussion

Using *in silico* approaches to screen promising compounds in the early-stage of R&D is not only possible, as demonstrated in this case study, but also beneficial from multiple perspectives. It is possible to first reduce the number of tested compounds through a categorisation approach, forming group of substances based on their expected MechoA and other parameters such as the structure. Once groups are formed, (Q)SARs results for a broad spectrum of toxicological endpoints can be obtained for representative substances of each group, leading to consensus results for each endpoint. This in turn can provide enough information on the target endpoints to identify the advantages or drawbacks of certain groups of compounds based on toxicological predictions.

The workflow used in this case study can be applied again for the same purpose for further in-depth development. Additionally, using the MechoA Premium scheme, the initial classification can be achieved for a very broad range of organic compounds since the scheme covers mechanisms of toxic action for both environmental and mammalian toxicology applicable to tens of thousands of substances. Furthermore, the methodology can be adapted to many endpoints ranging from environmental toxicology to human toxicology.

Conclusion

From these results, the selection of promising group of structures (i.e. substances of low level of concern for human health while maintaining properties of interest) was facilitated. Incorporating toxicological assessment at an early stage in R&D not only reduced the need for experimental studies, animals, time and cost but also the risk of regrettable substitution.

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[1] iSafeRat® Desktop v4.0, 2022 for High Accuracy QSAR prediction by KREATiS SAS (https://isaferat.kreatis.eu/)
[2] MechoA+ scheme publication in progress
[3]F. Bauer, P. Thomas, S. Fouchard, N. Serge, High-accuracy prediction of Mechanisms of Action using structural alerts, Computational Toxicology 7 (2018).

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