A quick and efficient method as part of a process to develop new safe and sustainable by design substances

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INTRODUCTION

To ensure a brighter future for the next generations, **innovative approaches** are needed to **develop safe and sustainable molecules** from scratch. The method proposed could help industry R&D meet this obligation by lifting the (eco)toxicological perspective to the first line of product evaluation rather than the last one as has typically been the situation till today. The method has application in all chemistries, from pharmaceuticals, speciality chemicals and cosmetics to the agrochemicals. To assist in the design optimisation of new compounds, direct collaboration with industry R&D is needed. A workflow developed by the KREATiS expert team has already been successfully applied in several cases to companies in the fragrance, general chemical and agrochemical industries to refine their molecules before stepping into the complicated and expensive world of regulatory dossier submission. Using available *in silico* tools, such as iSafeRat® Desktop and its many (Q)SAR models as well as other *in silico* tools, the team sets out below a scheme to customise a workflow to fast track product safety assessment using an ensemble of available tools and expert opinion from a multi-disciplinary team.

Goal

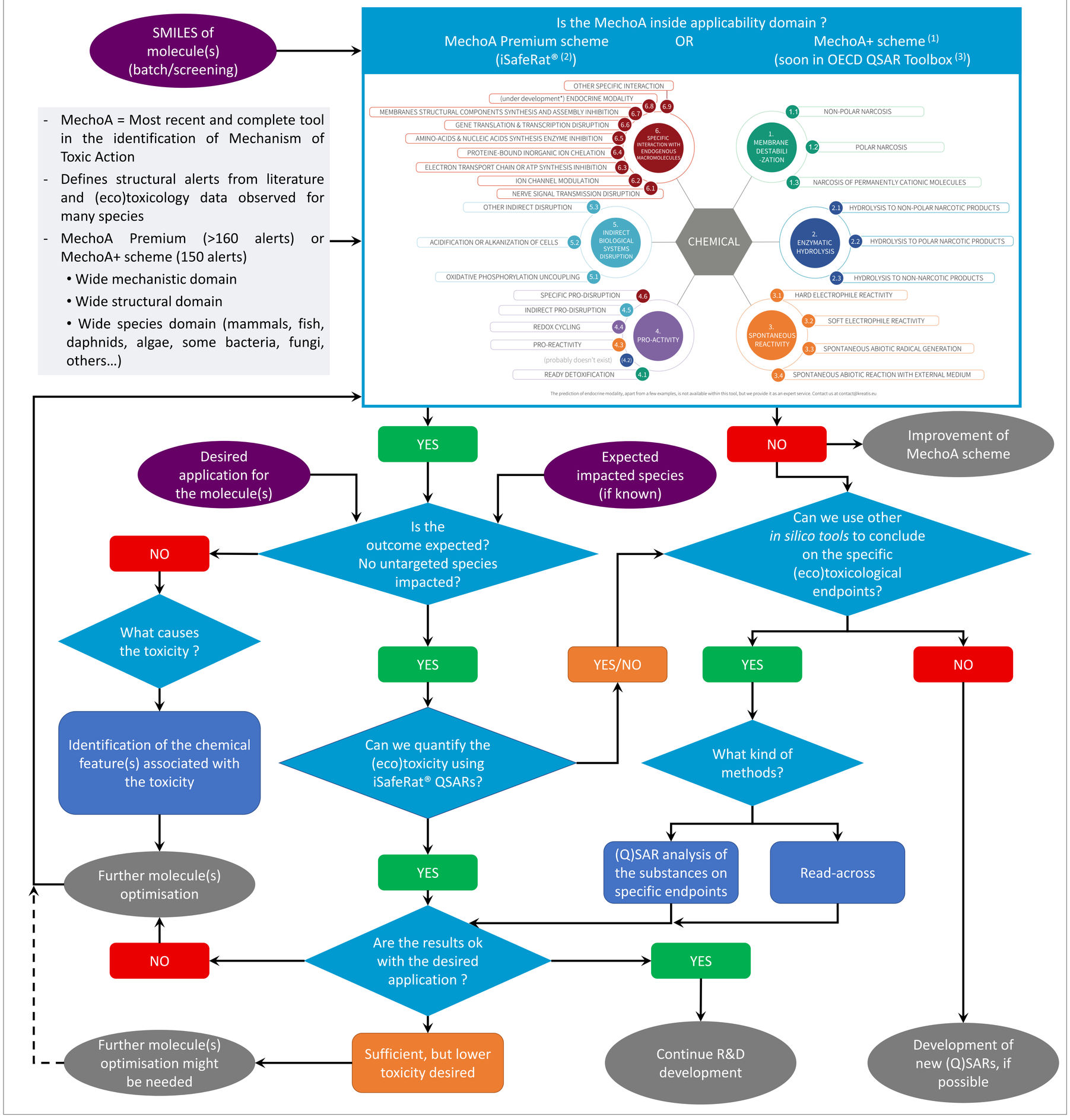
To design new, safer chemicals, it is necessary to identify critical endpoints for which the investigated molecules could fail during the process of development. Looking from an (eco)toxicological perspective, unexpected Mechanisms of toxic Action (MechoA), could lead to high toxicity for given species leading to downstream restrictions on use or even dossier refusal. The aim of this workflow is to detect these problems in advance using *in silico* tools that are reliable and fast enough to improve the decision-making process.

The workflow in brief

The workflow is designed to provide a first-hand general overview for most (eco)toxicological endpoints (e.g. aquatic ecotoxicity, biodegradation, skin sensitisation). It is established using iSafeRat® and other (Q)SARs (*in silico* tools) with known applicability domains. The first step of the workflow is the Mechanism of Toxic Action (MechoA) scheme. If a molecule(s) fall(s) within its applicability domain, this profiler is key to understand the molecular mechanism(s) responsible for (eco)toxicity, to identify chemical feature(s) associated with (eco)toxicity and species of concern. It integrates a large set of structural alerts and can identify unwanted toxic mechanisms. Then, a decision tree guides the user to obtain additional information from various (Q)SAR models and better characterise the (eco)toxicity of molecule(s). This set of information allows the user to rethink the design of its chemical candidate(s).

After repeated application of the workflow, toxic effects should decrease while preserving intended properties. The workflow applies to single substance notification and high throughput screening to select the best-in-class candidate from an HSE perspective.

A versatile workflow to adjust physico-chemical, environment and human health properties



CONCLUSION

Given the generality of the method, the workflow presented here is applicable for a large variety of substances and endpoints. Thanks to its multiple strengths, they are many ways for this approach to be a useful strategy in SSbD methodology. Using *in silico* predictive tools to estimate the relative toxicity of a new compound in early-stage research can save time and money. It is indeed much cheaper than experimental tests and more ethical as it respects the 3Rs paradigm. It can also identify weaknesses ahead and prevent future issues as well as provides key information for regulatory dossiers. The improvement of different tools and knowledge will make this workflow even more reliable in the coming years.

REFERENCES

(1) MechoA+ scheme publication in progress
(2) iSafeRat® Desktop v4.0.39, **2023** for High Accuracy QSAR prediction by KREATiS SAS (https://isaferat.kreatis.eu/)
(3) OECD QSAR Toolbox (v4.5 SP1), **2022** (QSAR Toolbox)

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