Predicting nuclear receptor activity of chemicals using a suite of complementary in silico methods for endocrine disruption hazard identification

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INTRODUCTION

It is suspected that endocrine-disrupting chemicals cause adverse effects in the endocrine system by interfering with the synthesis, transport, degradation, or action of endogenous ligands. In 2018, ECHA and EFSA published guidance describing how to perform hazard identification with respect to endocrine-disrupting properties by following the scientific criteria which are outlined in Commission Delegated Regulation (EU) 2017/2100 and Commission Regulation (EU) 2018/605 for biocidal products and plant protection products, respectively. In this guidance, computational approaches are proposed as a line of evidence for endocrine activity assessments. An in silico screening protocol for endocrine disruption which follows this guidance is described.

METHODOLOGY

An in silico protocol to be applied in the first step of the assessment strategy was developed. It addresses EATS (Estrogen, Androgen, Thyroid, Steroidogenesis) and 'other' modalities as well as the Mode of Action agonist, antagonist or binding. The protocol combines predictive models developed with different methodologies: QSAR models of receptor-based activity, profilers based on structural alerts and decision trees, 3D molecular modelling and ToxCast Pathways models. All the models are applied and the results are combined. If the substance is included in the training set of a model, we use both the predictions and the experimental data. The results of the QSAR are rated according to the sensitivity of the model and the reliability of the prediction to consider both the uncertainty of the model itself and the uncertainty of the prediction. The results of the profilers are primarily used to confirm the results of the QSAR as these approaches are known to yield a high rate of false positives. The molecular modelling and the in-vitro ToxCast results are rated according to the reliability of the models only as the applicability domain is not an issue.

RESULTS

Two examples are demonstrated: butylparaben and triclosan.

Butylparaben, known to be active towards the oestrogen receptor, is predicted, with a high probability, to be an ED with an estrogen modality and an agonist mode of action. No other relevant effects are predicted.

Triclosan, known to be active towards the androgen receptor, is predicted, with a high probability, to be an ED with an androgen modality and an antagonist mode of action. A low probability of action with a thyroid modality is also predicted.

DISCUSSION

Our in silico screening protocol combines the results of 117 models and is able to predict the potential of a chemical to initiate an ED pathway with EATS modalities providing a hypothesis on the active modality and the MoA. The in silico prediction provides strong evidence for either deprioritisation or prioritisation for further testing. External validation of the protocol is under way, with results expected by summer 2022. The protocol will be fully implemented in KNIME in order to avoid any transcription errors. KNIME is an open-source analytics platform for creating and designing data science workflows and reusable components accessible to everyone.