Establishing best practices for endocrine disruption assessments

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INTRODUCTION

There is growing concern about the possible adverse effects of Endocrine Disrupting Chemicals (EDCs) because they can mimic the interaction of natural hormones and alter their endogenous pathways. The possible consequences of this include developmental malformations (Mattiske D M. and Pask A J., 2021), metabolic disorders (Magueresse-Battistoni B. et al., 2017) and increased risk of cancer (Parron et al., 2014).

These concerns were reflected in the EU 2017/2100 and EU 2018/605 regulations for biocidal products and pesticides. While human and wildlife exposure to EDCs is not limited to these products these regulations need to be extended and data integrated to include other products in order to minimise the risk.

A widespread hazard identification for endocrine-disrupting properties needs to develop rapid, cost-effective and reliable tools able to screen an extremely high number of molecules, in addition to standardised criteria to interpret the results.

We intend to develop a standardised in silico protocol to predict endocrine disruption, one which combines three different approaches: structural alerts, QSAR models and molecular docking, and implement it in a prediction suite.

METHODOLOGY

Our proposal is to combine three different in silico approaches to determine different aspects of endocrine disruption.

The first approach is the identification of structural alerts, which are molecular substructures associated with a determined activity. The main problem with this type of approach is that a negative prediction is totally inconclusive.

The second approach is the application of QSAR models. These models will cover three different aspects for each individual nuclear receptor analysed: the capacity of binding to the receptor, the capacity to act as an agonist and the capacity to act as an antagonist. The NURA dataset is used to generate these QSAR models (Valsecchi C. et al., 2020).

Lastly, previous results will be complemented by molecular docking models. These models will take known agonists and antagonists into account in order to interpret the results more effectively.

RESULTS

We are currently developing QSAR models for estrogen receptor (ER) alpha for the three endpoints mentioned above (binding, agonism and antagonism). Moreover, we have already implemented the most important structural alerts described in the literature and we are defining the molecular docking steps in order to implement them in an automated workflow. The next step will consist in developing the prediction suite and extending the prediction to include other receptors.

DISCUSSION

The ultimate aim of this work is to establish a thorough in silico hazard identification protocol that integrates the three complementary techniques, where each of them will have a weight in the global prediction.