P03-14 Predicting nuclear receptor activity of chemicals using a suite of complementary *in silico* methods for endocrine disruption hazard identification

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BACKGROUND

Endocrine-disrupting chemicals are suspected to cause adverse effects in the endocrine system by interfering with the synthesis, transport, degradation, or action of endogenous ligands. In 2018 a guidance describing how to perform hazard identification for endocrine-disrupting properties by following the scientific criteria which are outlined in EU 2017/2100 and EU 2018/605 for biocidal products and plant protection products, respectively, was published by ECHA and EFSA. In this guidance computational approaches are proposed as line of evidence for endocrine activity assessment.

- ✓ There is a need for a widespread assessment of endocrine disrupting (ED) properties.
- ✓ There is a need for new approach methodologies (NAMs) to identify ED chemicals.

OBJECTIVES

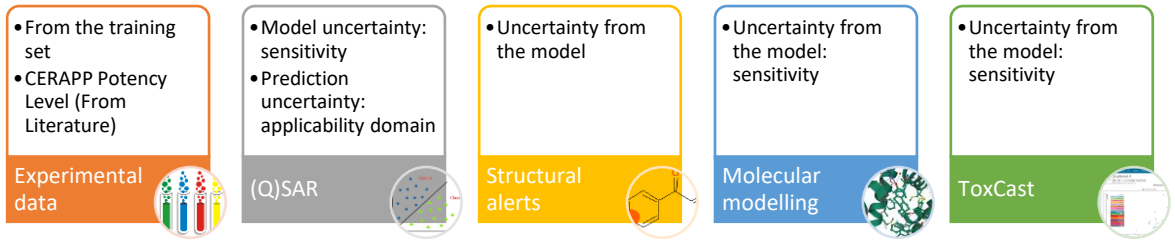
- ✓ To develop an *in silico* method suitable to be applied in the first step of the assessment strategy "*Gather all relevant information informing about endocrine modes of action*".
- ✓ To address EATS (Estrogen, Androgen, Thyroid, Steroidogenesis) and "other" modalities.
- ✓ To address the Mode of Action (MoA) agonist, antagonist or binding.
- ✓ To combine 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.
- ✓ To rate the predictions considering the uncertainty of the models and the uncertainty of the predictions.

METHODS

number of models		Modality				
		E	A	T	S	Other
MoA	Agonism	8	4	X	1	6
	Antagonism	4	3	X	1	X
	Binding	24	10	16	4	36
Methods	QSAR	21	11	12	1	27
	Modeling	4	2	2	3	7
	Profilers	8	1	2	2	8
	ToxCast	3	3	X	X	X

- ✓ 117 models addressing the same modality from different perspectives to increase the confidence in the outcome.
- ✓ Free and commercial tools.
- ✓ Training sets generally based on gene reporter assays, thus focus on molecular initiating events or cellular response.
- ✓ The prediction is an useful indication for potential endocrine activities.

ELEMENTS OF THE COMBINATION OF PREDICTIONS

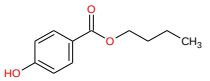


All the models are applied and the results are combined. If the substance is included in the training set of a model, we use both the predictions and the experimental data. The results of the QSAR are rated according to the sensitivity of the model and the reliability of the prediction to consider both 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 give high rate of false positives. The molecular modelling and ToxCast results are rated according only to the reliability of the models as the applicability domain is not an issue. If the final result is uncertain, a read-across can be applied.

RESULTS

number of models		Modality				
		E	A	T	S	Other
MoA	Agonism	positive	negative	X	negative	negative
	Antagonism	uncertain	uncertain	X	negative	X
	Binding	positive	negative	negative	negative	negative
Methods	QSAR	positive	negative	negative	negative	uncertain
	Modeling	negative	uncertain	negative	negative	negative
	Profilers	uncertain	negative	negative	negative	negative
	ToxCast	positive	negative	X	X	X

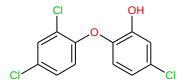
CAS 94-26-8
Butylparaben



Butylparaben, known to be active towards the estrogen 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.

number of models		Modality				
		E	A	T	S	Other
MoA	Agonism	negative	negative	X	uncertain	negative
	Antagonism	negative	positive	X	negative	X
	Binding	negative	positive	negative	negative	negative
Methods	QSAR	negative	positive	uncertain	negative	uncertain
	Modeling	negative	uncertain	uncertain	uncertain	negative
	Profilers	uncertain	negative	negative	negative	negative
	ToxCast	negative	positive	X	X	X

CAS 3380-34-5
Triclosan



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 to act with a thyroid modality is also predicted.

CONCLUSIONS

- ✓ 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 an 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 underway, with results expected by summer 2022.
- ✓ The protocol will be fully implemented in KNIME to avoid possible transcription errors.