An *in silico* battery to rule out chemicals with no endocrine disrupting potential on known targets

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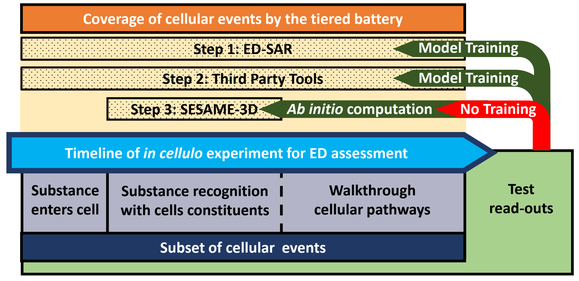
INTRODUCTION

- The number of chemicals to which we are exposed is increasing, leading to serious health issues. According to the EU Commission, there is a need for a widespread assessment of endocrine disrupting (ED) properties.
- Methods in the new and proposed regulations are time consuming and expensive.
- **The potential for ED is primarily dependent upon the capacity of a chemical to form a ligand-protein complex. No complex ➔ no ED modality.**
- An *in silico*, 3-step battery (Fig. 1) is described which can detect both ED potential, or lack of it, on known targets of estrogenic, androgenic, thyroidal and steroidogenic (EATS) modalities (and beyond).

Figure 1: the 3-step battery and how it covers the *in vitro* testing timeline



METHODS

3 methods designed to form the test battery:

1. ED SAR
   - Internally developed 2D structural alert scheme
   - Based on high throughput *in vitro* data on more than 8000 substances
   - Each assay result is validated upon solubility limit and viability of the cells
2. Consensus of Third Party Tools
   - A set of 32 external structural alerts models available in OECD QSAR Toolbox, Danish QSAR Database, VEGA and T.E.S.T from US EPA
   - The reliability of all models is assessed and a consensus prediction is made based only on expert judgement of reliable predictions
3. SESAME-3D (3D docking tool)
   - In-house developed workflow including various molecular modelling software
   - Unrestricted application domain within the space of organic chemistry
   - Quantitative prediction of interaction potency of chemicals with EATS targets

An *in silico* battery to predict potential for binding to studied EATS targets can provide **strong evidence to allow deprioritisation of organic chemicals**

Downstream testing can then be focussed on substances with endocrine activity alerts

No ED modality on known targets (EATS) predicted

=> low risk of endocrine disruption

=> low priority for further testing

Potential ED modality predicted

=> endocrine disruption cannot be excluded

=> further testing recommended (in vitro/in vivo)

Table 1: list of endpoints currently assessed by each tool in the battery

Biological target	Gene symbol	ED SAR	Third Party Tools	SESAME-3D
Estrogen Receptor α	ESR1	A+/A-	B/A+/A-	B
Estrogen Receptor β	ESR2	A+/A-	B/A+/A-	B
Androgen Receptor	AR	A+/A-	A+/A-	B
Thyroid Hormone Receptor α	THRA	A+/A-	B	B
Thyroid Hormone Receptor β	THRB	A+/A-	B	B
Thyroperoxidase	TPO	I-	-	-
Sodium-Iodide Symporter	SLC5A5	I-	-	-
Thyroid-Stimulating Hormone Receptor	TSHR	A+/A-	-	-
Iodothyronine Deiodinase I, II and III	DIO1, DIO2 and DIO3	I-	-	-
Progesterone Receptor	PGR	A+/A-	-	B
Follicle-Stimulating Hormone Receptor	FSHR	A-	-	-
Aromatase	CYP19A1	I-	-	-
Pregnane X Receptor (beyond EATS)	NR1I2	-	B	-

Footnote: 'B' = Binding ; 'A+' = Agonism ; 'A-' = Antagonism ; 'I-' = Inhibition ; '-' = not covered by this method

References: ED SAR and SESAME-3D are part of the KREATiS iSafeRat® model suite

RESULTS

1. ED SAR
   - Covers 17 EATS endpoints (see Table 1)
   - The overall accuracy for all endpoints and all structural alerts is of 99.6%, based on the training set
2. Consensus of Third-Party Tools
   - Covers 7 EAT endpoints and 1 non-EATS endpoint (see Table 1)
   - The accuracy of the employed models is within 64% and 90%, based on the respective training sets
3. SESAME-3D
   - Covers 6 EATS endpoints (see Table 1)
   - Accuracy: binding affinities (K_d) for native hormones are reproduced with an error < 10 nM vs. experimental references.

➢ The proposed methodology allows derivation of a consensus prediction of the potential of a chemical to initiate an ED phenomenon with EATS modalities. External validation of the battery is in progress, first results by summer 2021.

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