INTEGRATED COMPUTATIONAL NAM BASED ON MOLECULAR INITIATING EVENTS (MIES) AND PBK PREDICTIONS FOR EVALUATION OF THE STEATOGENIC POTENTIAL OF CHEMICALS.

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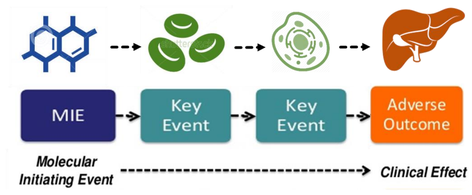
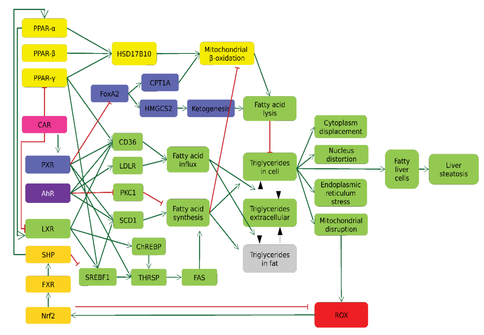
BACKGROUND

- *Chemical-induced non-alcoholic **hepatic steatosis** is a worldwide epidemiological concern.*
- *We propose **integrated computational NAMs** to assess the steatogenic potential of chemicals, accounting for both **toxicodynamics** and **toxicokinetics.***
- *Toxicodynamics was based on the predictions of **molecular initiating events (MIE)** of the **adverse outcome pathway (AOP)** of steatosis.*
- *Toxicokinetics was estimated with an **high-throughtput (HT) PBK model.***
- *Computational approaches were developed within the EU founded project **ONTOX** and were independently applied to classify the NAM Designathon compounds (131 out of 150).*
- *The two classifications were combined to return an overall classification for the **steatogenic potential of chemicals**.*



Graphical representation of the concept of Adverse Outcome Pathway (AOP).



Schematic depiction of AOP network leading to hepatic steatosis (AOPs 57, 34, 36, 60 and 61 from the AOPWiki).

MATERIALS & METHODS

1 NAM-BASED TOXICODYNAMICS – MIE ACTIVITY QSAR

a ***QSARs to predict MIEs of steatosis** were trained on inhibition data from ChEMBL v33. Activity data were converted to binary categories (threshold IC50 =10,000 nM).*

1. ***Multi-tasking (MT) model:** simultaneous modelling of multiple endpoints to improve the final predictions.*

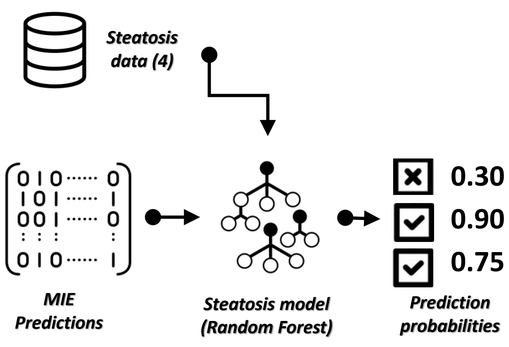
PXR | AhR | LXR | PPARα | PPARγ

2. ***Machine learning (ML) models:** individual QSAR based on ML and data transformation methods (feature selection with VSURF [2] and SMOTE [3]).*

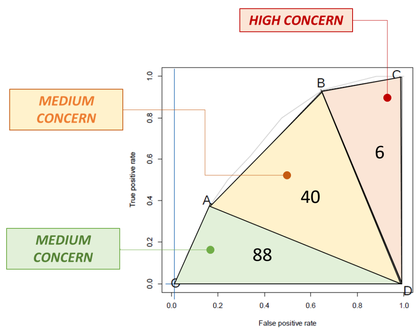
PXR* | AhR | LXR* | PPARα | PPARγ

**low performance, discarded*

b *A **random forest (RF)** model was trained on steatosis data. Predictions of the MT and ML models were used as **independent variables** to weight the contribution of each MIE to the final steatogenic outcome.*



c ***Prediction probabilities** of the RF were used to build a ROC curve.*
*The **ROC curve** was partitioned into three triangles, so that the sum of their areas maximizes the **area under the ROC (AUC).***
*Probability thresholds determined by the partition were used to classify the chemicals into **low**, **medium** and **high** risk.*



Activity classification of the EPAA compounds based on the steatosis predicting RF model

2 NAM-BASED TOXICOKINETIC – HT PBK MODEL

a ***High troughtput PBK models (HT-PBK)** were developed with the freely available, open-source modelling software **PK-Sim.**[(5)] HT-PBK was used to predict systemic availability.*

b *The HT-PBK model is parameterised with chemical input properties (**physicochemical and ADME**) predicted with various computational tools:*

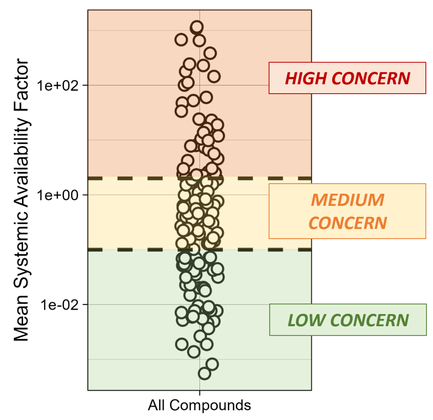
- *Water solubility*
- *Caco-2 permeability*
- *Human intrinsic hepatic clearance*
- *Fraction unbound to plasma proteins*

- *Distribution coefficient (logD) @pH =7.4*
- *Caco-2 permeability*
- *Plasma cearance*

- *Acidic and basic dissociation constant (pKa)*

- *Total cearance*

- *Distribution coefficient (logD) @pH =7.4*
- *Membrane affinity*



Bioavailability classification of the EPAA compounds based on the HT-PBK predictions

$$SAF^{*} = \frac{\text{Amount in the body (24h after last administration; after 5 years)}}{\text{Average Daily Dose}}$$

- *SAF (mean) > 200% = **high systemic availability.***
- *10% < SAF (mean) < 200% = **medium systemic availability.***
- *SAF (mean) < 10% = **low systemic availability.***

** Systemic availability factor redicted by the HT-PBK model*

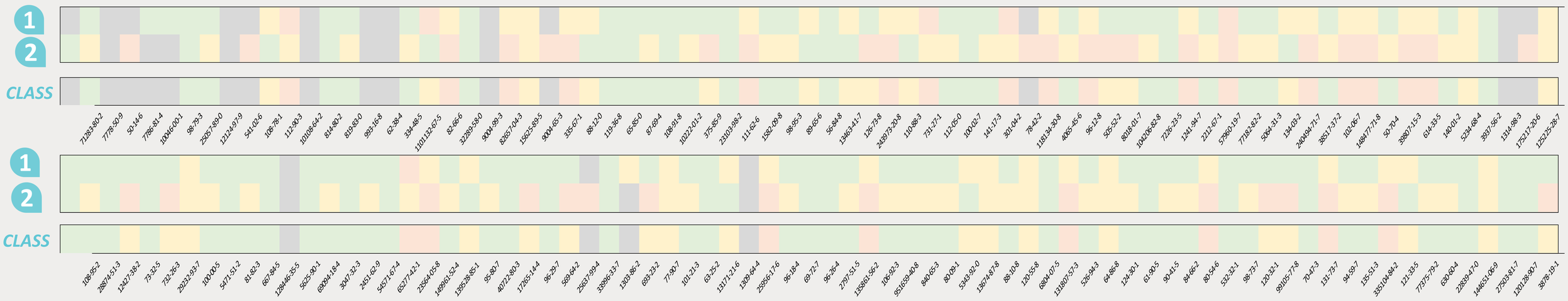
Additional details in the 'High-throughput Physiologically-based Kinetic (HT-PBK) modelling' case study report

RESULTS

*Toxicodynamics (1) and toxicokinetics (2) classifications were integrated to determine the final risk category (**CLASS**).*

- LOW CONCERN
- MODERATE CONCERN
- HIGH CONCERN
- NOT CLASSIFIED

2 Potential systemic availability (toxicokinetics)	1 Activity (toxicodynamics): High	Medium	Low
High	1	20	12
Medium	4	9	42
Low	1	10	32



References

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