The Final EUTOXRISK Symposium 2

Computational prediction tools used and developed in the project (WP3)

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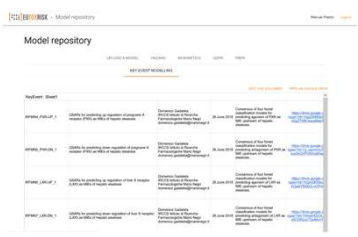
Coordinated by: UPF

Background Information

Existing knowledge can be used to predict biological properties of unknown compounds.

Substances of known biological properties can be characterized using their chemical structure, physico-chemical properties or gene expression.

Machine learning methods use this information to build a mathematical model describing the relationship between these features and substance biological properties.



Here we present a small sample of the technologies and models developed in EU-ToxRisk.

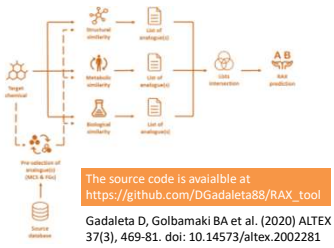
All models developed in the project, documented and with links to the data and model implementation were deposited in an online repository.

Technologies

Integrated Similarity-based Workflow For Automated Chemical Read-across

IRFMN developed a workflow for read-across analogue(s) selection based on the integration of different similarity metrics:

- Structural similarity, based on extended fingerprints and Tanimoto
- Metabolic similarity, accounting for common metabolic pathways
- Biological similarity, accounting for common biological assays



Gadaleta D, Golbamaki BA et al. (2020) ALTEX 37(3), 469-81. doi: 10.14573/altex.2002281

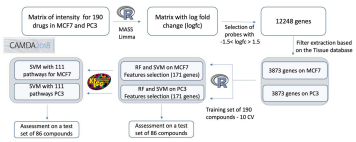
The workflow generates a ranked lists of analogue(s) for each similarity.

Analogues in multiple lists are prioritized.

Qualitative Gene expression Activity Relationship (QGexAR) approach to assess the risk of DILI

Computational tools able to predict Drug-Induced Liver Injury (DILI) based on gene expression data from *in vitro* assays remain a challenge.

UCPH introduced a Qualitative Gene expression Activity Relationship (QGexAR) approach to assess the risk of DILI for any chemical.



Aguayo-Orozco A. Brunak S, Taboureau O. (2021) Comp Tox. 17. 100147. doi: 10.1016/j.comtox.2020.100147

A classification model with a high performance (MCC of 0.74) was developed and validated with MCF7 data.

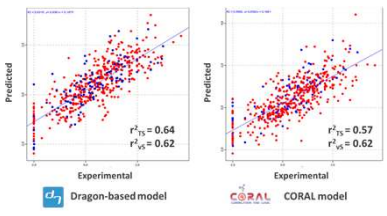
Application examples

Modelling of Plasma Protein Binding

IRFMN developed QSAR models to predict plasma protein binding (PPB).

Fraction unbound (FU) data for 670 drugs were used for modeling.

FU was converted to logK for modelling purposes. $\text{Log K} = \log \frac{1 - fu}{fu}$

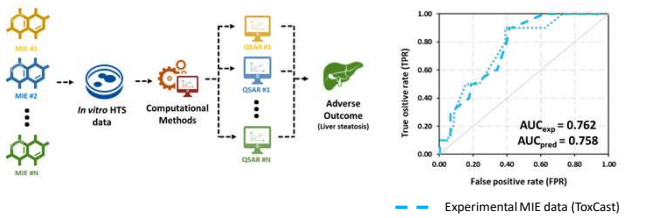


Toma C, Gadaleta D et al. (2019). Pharm Res, 36(2), 1-9. doi: 10.1007/s11095-018-2561-8

Structure-Activity Relationships for Molecular Initiating Events of Hepatic Steatosis

IRFMN and INERIS developed QSARs predicting the ability of chemicals to activate single molecular initiating events upstream of hepatic steatosis.

ToxCast in vitro HTS data was used to model relevant transcription factor (TF) activation. Nine endpoint for six TFs were selected for modeling: *PPARa_up, PPARg_up, AHR_up, AHR_dn, NRF2_up, LXR_dn, LXR_up, PXR_up, PXR_dn*.



Gadaleta D, Manganelli S, et al. (2018). JCIM, 58(8), 1501-1517. doi: 10.1021/acs.jcim.8b00297

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www.eu-toxrisk.eu/