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QSAR Models for Constitutive Androstane Receptor (CAR) Activation and Inhibition, and Screening of a Large Set of Environmental Chemicals

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CAR is a member of the nuclear receptor superfamily. In humans, this protein is encoded by the NR1I3 gene (nuclear receptor subfamily 1, group I, member 3). Together with the Pregnane X Receptor (PXR), for which the DTU QSAR team has previously developed QSAR models[1], CAR plays a major role in the detoxification of xenobiotic substances by upregulating the expression of proteins responsible for the metabolism and excretion in response to their presence. Examples of CAR-regulated genes are members of the CYP2B, CYP2C, and CYP3A subfamilies, sulfotransferases, and glutathione-S-transferases.

However, induction of these metabolizing enzymes alters not only the metabolism of the xenobiotic substances that induce them, but also alters the metabolism of various endogenous hormones such as thyroid and steroid hormones. This may increase their turnover leading to decreased levels in the body. As even moderate changes in maternal or fetal thyroid hormone levels may give irreversible neurological deficits in the offspring, such interference in the regulation of endogenous hormones may have negative consequences. Likewise, inhibition of CAR may lead to a decreased metabolizing potential in the body giving a decreased turnover of endogenous hormones as well as decreased detoxification and excretion of xenobiotics, such as endocrine disrupting chemicals.

Recently, high-throughput screening assays for CAR activation and inhibition were developed and used to screen almost 10,000 Tox21 chemicals. In this study, we used data from the qHTS assays to develop and validate Quantitative Structure-Activity Relationship (QSAR) models for CAR activation and inhibition in the Leadscope ® Predictive Data Miner software. The results will be presented.

[1] Rosenberg et al. “QSAR development and profiling of 72,524 REACH substances for PXR activation and CYP3A4 induction”. *Computational Toxicology* Vol. 1 (2017): 39-48.

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Section

	(Q)SAR models for regulatory use
X	Models for human health effects
	Models for ecotoxicological and environmental effects
	Protein-ligand interactions, *in silico* studies related to toxicological effects
	Software and tools

Presentation

	oral
X	Poster