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A QSAR Model for Thyroperoxidase Inhibition and Screening of a Large Set of Environmental Chemicals

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Introduction

Thyroid hormones (THs) are critical modulators of a wide range of biological processes from neurodevelopment to metabolism. Well-regulated levels of THs are critical during development and even moderate changes in maternal or fetal TH levels produce irreversible neurological deficits in children. The enzyme thyroperoxidase (TPO) plays a key role in the synthesis of THs (Figure 1). Inhibition of TPO by xenobiotics leads to decreased TH synthesis and, depending on the degree of synthesis inhibition, may result in adverse developmental outcomes.

Recently, a high-throughput screening assay for TPO inhibition (AUR-TPO) was developed and used to screen the ToxCast Phase I and II chemicals [1].

In the present study, we used data from the AUR-TPO to develop and validate a Quantitative Structure-Activity Relationship (QSAR) model for TPO inhibition.

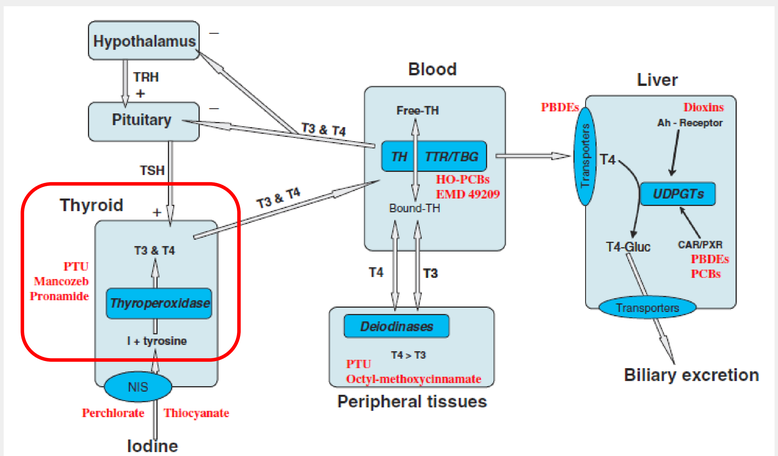

Figure 1. Overview of the thyroid hormone control pathways with focus on TPO's role in TH synthesis (red square). Modified from [2].

Materials and Methods

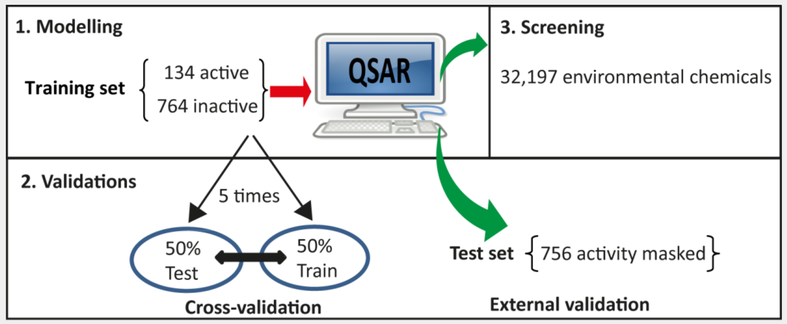

Figure 2. Modelling, validation and screening steps. Red arrow indicate model building, green arrows indicate application of the model.

Training set. 898 discrete organic chemicals from US EPA ToxCast phase I and II with experimental results from the AUR-TPO.

Modelling. A categorical QSAR model for inhibition of TPO was developed using Leadscope [3]. For predictions to be within the applicability domain (AD) of the model it was required that an active prediction had a predicted probability ≥ 0.7 and an inactive prediction had a predicted probability ≤ 0.3.

Cross-Validation. A five times two-fold cross-validation was performed within the model's defined AD.

External validation. After the model was built 756 discrete organic chemicals from the US EPA Endocrine Disruption Screening Program (EDSP21) with masked experimental AUR-TPO results were predicted and predictions within the model's AD were compared to the AUR-TPO results by US EPA.

Screening. A US EPA collection of 32,197 environmental chemicals to which humans are potentially exposed was screened through the QSAR model to predict the potential for these chemicals to inhibit TPO.

Conclusions

A QSAR model for inhibition of TPO with balanced accuracy of 78.8% and 85.7% in cross-validation and external validation, respectively, was developed (Table 1). The model identified 15,391 (47.8%) of the 32,197 environmental chemicals to be within its applicability domain, and of these 3786 (24.6%) chemicals were predicted to be positive for TPO inhibition (Table 2). Results from this screening can be used in a tiered approach to prioritize possible thyroid disrupting chemicals (TDCs) for further evaluation.

Results

Table 1. Coopers statistics results in the cross- and external validation.

	In AD, %	Sensitivity, %	Specificity, %	Balanced Accuracy, %
Cross-validation	50.4	75.6	81.8	78.8
External validation*	51.1	87.3	84.1	85.7

* 386 of the 756 test compounds had predictions inside the AD, 47 of these were inconclusive in test. Predictions were compared to 63 active and 276 inactive experimental results for the performance measurements.

Table 2. Screening results for the 32,197 environmental chemicals for TPO inhibition.

	In AD	Predicted active	Predicted inactive
n	15,391	3786	11,605
%	47.8	24.6	75.4

Disclaimer: The views expressed in this poster are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

[1] Paul Friedman et al. (2016) Tiered High-Throughput Screening Approach to Identify Thyroperoxidase Inhibitors within the ToxCast Phase I and II Chemical Libraries. *Toxicological Sciences*, online February 15.
[2] Crofton, K.M. (2008) Thyroid disrupting chemicals: mechanisms and mixtures. *International Journal of Andrology* 31, 209–223
[3] Leadscope Predictive Data Miner, Leadscope Enterprise version 3.2.4-1, Leadscope, Inc., http://leadscope.com.