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

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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. 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. In the present study, we used the results from the AUR-TPO screening to develop a Quantitative Structure-Activity Relationship (QSAR) model for TPO inhibition in Leadscope®. The training set consisted of 898 discrete organic chemicals: 134 positive and 764 negative for TPO inhibition. A 10 times two-fold 50% cross-validation of the model was performed, yielding a balanced accuracy of 78.7% within its defined applicability domain. More recently, an additional ~800 chemicals from the US EPA Endocrine Disruption Screening Program (EDSP21) were screened using the AUR-TPO assay. This data was used for external validation of the QSAR model, demonstrating a balanced accuracy of 85.7% within its applicability domain. Overall, the cross- and external validations indicate a model with a high predictive performance. Next, we used the QSAR model to screen 32,197 environmental chemicals to which humans are potentially exposed. The model could predict 15,391 (47.8%) of the chemicals within its applicability domain, and of these 3786 (24.6%) chemicals were predicted to be positive for TPO inhibition. Predictions from this screening can be used in a tiered approach to prioritize putative thyroid disrupting chemicals (TDCs) for further evaluation. *This abstract does not necessarily reflect U.S. EPA policy*