# EXPLORING LIGAND AND STRUCTURE BASED MODELING FOR ENDOCRINE-DISRUPTING RESPONSE PREDICTION OF PER-AND POLYFLUOROALKYL SUBSTANCES

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**Abstract:** Exposure to poly- and perfluoroalkyl substances (PFASs), an emerging class of endocrine disrupting halogenated pollutants, has been linked to thyroid toxicity in human populations across the globe. The PFASs can compete with thyroxine (T4) for binding to the human thyroid hormone transport protein transthyretin (TTR) which may lead to reduce thyroid hormone levels leading to endocrine disrupting activity. Distress about their environmental fate and endocrine-disrupting activity has initiated several research projects, but the amount of experimental data available for these pollutants is limited. In this background, twenty-four PFASs, together with 6 structurally similar natural fatty acids binding capacity in a radioligand-binding assay values were modeled with classification- and regression-based quantitative structure-toxicity relationship (QSTR) tools using simple molecular descriptors obtained from chemical structures of the compounds to identify the responsible structural features and fragments of these diverse classes of PFASs. Additionally, docking study performed employing the crystal structure complex of TTR with bound 2,´6´-difluorobiphenyl-4-carboxylic acid (PDB: 2F7I) to constitute the receptor model for human TTR provided corroborating evidence for these binding interactions and indicated multiple high-affinity modes of binding. The developed *in silico* models therefore provide an understanding of important structural attributes of these chemicals and may provide important information for the design of chemicals for future synthesis of molecules as well as may serve as an efficient query tool for screening of large databases with diminished systemic toxicity profile. The study will be extended to mixture toxicity prediction in future with new approaches.

**Keywords:** Docking, Endocrine disruption, PFASs, QSAR, Thyroid hormone, Thyroxine, Transport protein transthyretin

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