Molecular Models of Environmentally Persistent Perfluorinated Chemicals in the Biological Milieu

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The Peroxisome Proliferator Activated Receptors (PPARs), a class of nuclear receptors that modulate both transcription and metabolic processes, are implicated in numerous pathological disorders (i.e. type-II diabetes and metabolic syndrome). It is known that the persistent environmental pollutants PFOA (perfluorinated octanoic acid) and PFOS (perfluorooctane sulfonate) are specific PPAR agonists in a wide variety of animal species. Despite in vivo toxicity studies in animals, the specific binding affinities and molecular mode of binding of this class of compounds to animal/human PPARs have not been evaluated. To this end, computational toxicological methods that screen putative toxicant and target systems at the molecular level are required to elucidate this information and should complement and enhance the Agency's task of evaluating the risk due to chemicals in this environmentally relevant class.

Employing a combination of molecular modeling and docking strategies, the relative binding scores for a homologous series of perfluorinated acids and sulfonates interacting with the ligand binding domain of three PPAR (α,β,γ) nuclear receptor (NR) isoforms were computed. Using similar methods, an affinity fingerprint matrix for the same perfluorinate series interacting with 15 additional NRs and specific cytosolic and extracellular transport proteins was generated (serum albumin, lipid binding proteins, and α2u-globulin). These *in silico* screens enabled target-specific rank ordering of the binding affinity of these perfluorinates relative (1) to each other, and (2) to other putative natural ligands and known anthropogenic nuclear receptor modulators.

Additionally, analysis of computed ligand docking scores, ligand-protein contacts, ligand-specific physico-chemical properties and comprehensive fluoroalkane / protein structural information from the literature allowed us to speculate and rationalize key features for perfluorinate specificities amongst these targets, and discuss some additional experimental procedures and aspects to verify these conclusions. [MRG is supported by EPA-DESE Training Agreement, EPA CR83323601. This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy]