**Peroxisome-Proliferator Activated Receptors as a Macromolecular Target for Chemical Toxicity: Models of the Interactions of PPARs with Perfluorinated Organic Compounds-S.**

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**Abstract**

The Peroxisome Proliferator Activated Receptors (PPARs), a class of nuclear receptors that modulate both transcription and metabolic processes, are implicated in a variety of metabolic disorders linked to lipidogenesis, adipose tissue accumulation, fatty-acid oxidation pathways, 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 animal species, the specific binding affinities of this class of compounds to animal/human PPARs have not been evaluated. In addition, the specific molecular modes of binding have not yet been identified. For these reasons, the use of molecular modeling methods to better understand the mode of action and estimate the relative binding affinities of PFOA, PFOS and other related chemicals in comparison to known agonist, antagonists and putative natural ligands of the PPARs will greatly facilitate the Agency's task of evaluating the risk due to chemicals in this environmentally relevant class.

Using computational molecular interaction modeling methods,

(A) Multi-fragment receptor mapping

(B) Homology modeling and Molecular docking studies

(C) High-throughput virtual screening

Polyfluorinated organic compounds (PFCs) and other similar chemicals were ordered relative to a variety of agonists/antagonists and putative natural ligands. Potential binding modes of chemicals in this class are determined and illustrated. These methods may be applied to other similar chemicals of unknown activity. Tools are being developed to more generally characterize the affinity and specificity of unknown ligands in the context of PPARs ($\alpha$,$\beta/\delta$,$\gamma$. isoforms) modulating potential. These approaches will provide a more efficient and effective prioritization scheme for studies of the binding of diverse test ligands of environmental significance for endocrine disrupting potential.

Many toxicological processes may be studied using the same paradigms as used in this study. As a result, methods applied here may have a far reaching effect for evaluating the risks of this and other classes of chemicals and other macromolecular targets. *This abstract does not necessarily reflect EPA policy.*

**Acknowledgement**

Michael-Rock Goldsmith is supported by NHEERL-DESE Cooperative Training in Environmental Research, **EPA CT829471**