Digging Deeper into Deep Data: Molecular Docking as a Hypothesis-Driven Biophysical Interrogation System in Computational Toxicology

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Developing and evaluating predictive strategies to elucidate the mode of biological activity of environmental chemicals is a major objective of the concerted efforts of the US-EPA's computational toxicology program. Aligning these strategies with the Agency's ongoing chemical-specific risk-assessment needs will provide additional molecular-level insight for decision-making purposes. The judicious use of varying combinations of *in vivo* (animal), *in vitro* (animal/human cell lines), epidemiological, chemical genomic, and pharmacokinetic (PK) studies have shed light on potential modes of toxicity for many (classes) chemicals of interest. Often, data required for extrapolations inherent in human risk assessment are unavailable. *In silico* methods used to provide information surrogates at the molecular level are vital complements to relevant toxicology data

Employing a virtual screening approach, a diverse set of chemicals (environmental, pharmaceutical and dietary) were computationally docked into multiple macromolecular targets (nuclear receptors, extracellular transport and cytosolic lipid binding proteins) using an exhaustive docking algorithm. The individual chemical-target poses, scores, and the chemical-protein contacts generated by this approach afforded a virtual affinity fingerprint matrix that provides mechanistic molecular-level insight. Knowledge gained from quantitative and visual analyses (ANOVA analysis, clustering/heat maps, and linkage networks) of these virtual screens demonstrate the utility of these approaches and their ability to resolve ligand panagonism and receptor promiscuity in addition to known affinity and activity differences between species or between tissues of a given species.

These virtual affinity fingerprint matrices coupled to tissue-specific receptor distribution data and inference mapping of downstream signal transduction elements provides a molecular level of accountability, and complements experimental high-throughput screening and toxicogenomic endeavors. [*This work does not reflect official EPA policy*]