Application of the *In Silico* Toxicant-Target Approach to Screening a Chemical Library for Estrogenicity

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In many mechanisms for the adverse effects of anthropogenic chemicals a critical and perhaps differential step requires the interaction of the chemical with a biological macromolecule. Where the macromolecular target is a receptor, this interaction may be studied by computationally docking the putative ligand into the receptor binding site. Environmental estrogenicity is an example of a process that can be modeled by this *in silico* approach.

In this study the capacity of a series of 318 chemicals to bind to the estrogen receptor has been evaluated using three different methods for docking. Each method depends on semi-empirical approaches to evaluate the interaction but varies in these specifics: 1) The method for the discovery of the best possible fit between the putative ligand and the receptor, 2) the determination of the energetics of each fit, 3) the semi-empirical atom based parameterization of the interaction. The data set studied contains 281 chemicals recently evaluated using a single rat uterine ER binding assay. This data set contains chemicals that bind much more weakly than estrogen and non-binders. In addition, 37 known strong binders were added. The protein targets were derived from known rER and hER crystal structures.

The result of the docking calculations is a list of chemicals ordered by their predicted affinity for rER. All of the experimental rER binding chemicals appear in the first 27% of the list but are not ordered by their binding affinity. The choice of demarcation between predicted binding and non-binding chemicals is determined by the balance between false positives and false negatives and will be discussed. These results suggest that this approach has value as a prescreen for setting testing priorities. *[This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.]*