The Toxicant-Target Paradigm for Toxicity Screening – Pharmacophore Based Constraints

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There is a compelling need to develop information for the screening and prioritization of the health and environmental effects of large numbers of man-made chemicals. Knowledge of the potential pathways for activity provides a rational basis for the preliminary evaluation of risk and the establishment of priorities for obtaining missing data. The differential step in many mechanisms for toxicity may be generalized as the interaction between a small molecule (a potential toxicant) and a macromolecular target. An approach based on computation of the interaction between a potential molecular toxicant and a library of macromolecular targets for toxicity (The Toxicant-Target approach) has been proposed as an element for toxicity screening. A library of 151 protein targets has been developed from consideration of the putative Toxcast Phase I protein targets and available crystal structures. In a previous study a target developed from the crystal structure of the estrogen receptor was capable of identifying weakly estrogenic molecules from a library of similar chemicals. The best results were obtained when simplified pharmacophore based constraints were used to limit the allowed ligand-target poses. These constraints were obtained from considering the potential hydrogen bonds in the crystal structures of the ligand-protein pairs. Similar constraints have been identified for the nuclear receptors in the 151 target library: 24% have 1 constraint; 65% have 2 constraints; 12% have 3 constraints. Since the goal is to identify all potential toxicant chemicals (both strong and weak binders), the best results are obtained when a minimized set of constraints is applied. In a tiered scheme for the prioritization of chemicals by their capacity to act at a specific target, the constraints may be best applied in an early tier and then reapplied when computing the strength of the interaction. [This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.]

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