Computational Molecular Modeling Methods for Screening for Chemical Toxicity: The Toxicant-Target Approach

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The risk posed to human health and the environment by chemicals that result from human activity often must be evaluated when relevant elements of the preferred data set are unavailable. Therefore, strategies are needed that estimate this information and prioritize the outstanding data requirements. Knowledge of the potential mechanisms for activity provides a rational basis for the extrapolations inherent in the preliminary evaluation of risk and the establishment of priorities for obtaining missing data for environmental chemicals. The differential step in many mechanisms of toxicity may be generalized as the interaction between a small molecule (a potential toxicant) and one or more macromolecular targets. An approach based on computation of the interaction between a potential molecular toxicant and a library of macromolecular targets of toxicity has been proposed for chemical screening. A library of potential protein targets for chemical toxicity has been developed from the Protein Data Bank (www.rcsb.org/pdb). As a test of this approach the interaction between targets constructed from the rat estrogen receptor and molecules in a data set of chemicals tested for the capacity to compete with the natural ligand for that receptor have been computed using molecular “docking” methods. These methods were developed to aid in the discovery of new pharmaceuticals (chemicals that bind strongly to the receptor). In this application they are being tested for their capacity to identify molecules that bind weakly to the receptor in a data base of primarily inactive chemicals. The data set being studied (KIERBL in DSSTox) contains 280 chemicals plus 17□-estradiol. Of these chemicals 14 compete with the natural ligand for the receptor and each binds 3-5 orders of magnitude more weakly than 17□-estradiol. Two different rapid computational “docking” methods have been applied. Using these without consideration of the geometry of binding between the toxicant and the target, all of the active molecules were discovered in the first 16% of the chemicals. When a filter is applied based on the geometry of a simplified pharmacophore for binding to the ER, the results are improved and all of the active molecules were discovered in the first 8% of the chemicals. In order to obtain no false negatives in the model that includes the pharmacophore filter only 8 molecules of the 280 are false positives. These results indicate that molecular “docking” algorithms that were designed to find the chemicals that act most strongly at a receptor can efficiently separate weakly active chemicals from a library of primarily inactive chemicals. The advantage of using a pharmacophore filter suggests that the development of filters of this type for other receptors will prove valuable for other potential targets. This approach may be used in conjunction with other molecular parameters and bioassay data to address chemical prioritization. The evaluation of the capability of these methods, or any multi-parameter method for chemical screening, requires an understanding of the position of an untested chemical in the parameter space of model. A method for determining this position in the space of relevant parameters is being developed.