Computational Docking of the Isomers of Nonylphenol to the Ligand Binding Domain of the Estrogen Receptor

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Nonylphenols are environmentally persistent endocrine disrupting chemicals. They exist in the environment as complex mixtures containing many nonylphenol isomers. Environmental mixtures of nonylphenols, along with a few single isomers have been tested for their capacity to interact with the estrogen receptor (ER) and have been shown to be weakly estrogenic. The few individual isomers tested have only in rare examples been shown to be more estrogenic than environmental mixtures of undetermined isomers. The capacity of a molecule to bind to ER depends on the three dimensional structure of the potential ligand. There are 211 geometric isomers and 551 stereo isomers of nonylphenol. The potential for each isomer to bind to ER will depend on the energetics the interaction. Computational molecular docking has been used to examine the capacity of each nonylphenol isomer to bind to ER. Computational targets have been created by removing the ligand atoms from crystal structures of ER-ligand complexes. The isomers of nonylphenol have been docked sucessfully into these targets. The results indicate that the potential for binding will be greatest when the molecular structure maximizes both the strength of the hydrogen bonds between the receptor and the phenolic hydroxyl group, and the steric interaction between the alkyl group and the hydrophobic core of the receptor. For some isomers the formation of the necessary hydrogen bonds forces the ligand-receptor complex into a structure with less favorable steric interactions. For example, branching at the alpha position decreases the interaction while branching in the beta and gamma positions often increases the interaction. Analysis of these considerations can provide insight for the design and manufacture of nonylphenol (and other alkylphenol) mixtures that minimize their potential estrogenicity. [This abstract does not necessarily reflect official Agency policy.]