Biophysical Models In Environmental Risk Assessment: Conazoles in the Human Context

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Considerable effort has been made to elucidate the off-target molecular mode-of-action (MOA) of conazole fungicides in the ongoing chemical-specific risk-assessment initiatives of the US-EPA. Combinations of *in vivo* (rat and murine), *in vitro* (human primary hepatocyte), chemical genomic, and pharmacokinetic (PK) studies have shed some light on potential off-target modes of toxicity and their associated ADME properties. However, extrapolations for off-target effects and molecular MOAs of conazole-class fungicides in the human context remain incomplete; *in silico* methods used to screen, extrapolate, and prioritize molecular modes of toxicity on actual human receptors are vital to complement current risk-assessment data on this class of chemicals. Employing a virtual screening approach multiple conazoles and their respective stereoisomer, tautomer, and metabolite isoforms were docked to the ligand binding domains of multiple macromolecular targets (nuclear receptors, extracellular transport and cytosolic lipid binding proteins) using an exhaustive docking algorithm. The individual toxicant-target poses, scores, and the ligand-protein contacts generated by this strategy afforded an affinity fingerprint matrix that provided a rational basis to obtain mechanistic molecular toxicological insight. We predict that chiral conazole fungicides have stereoselective affinity fingerprints in humans, a finding that corroborates with current animal study: based on our target selections this extrapolates to potentially profound stereospecific control of both pharmacodynamic and PK in humans. Our biophysical screening models provide a means to (1) elucidate receptor-specific stereoselectivity, affinity, and molecular MOA (2) complement the analysis of omics data in hypothesis-driven toxicogenomics, and (3) provide a data-rich framework for follow-up stereospecific experiments. [*This work does not reflect official EPA policy*]