AN EVALUATION OF TOXCAST ANGIOGENIC DISRUPTORS FOR EFFECTS ON MITOCHONDRIAL BIOACTIVITY PROFILES

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Angiogenesis is a critical developmental process and a potential target for chemical teratogenesis. Over one-tenth of the Tox21 library of 10,000 compounds have been shown to disrupt mitochondrial function [Attene-Ramos et al., 2015]. Previous studies utilizing ToxCast chemicals have shown a correlation between vascular disruption in *Tg(kdrl:EGFP)*^{mitfab692} zebrafish embryos and mitochondrial disruption reported in literature [McCollum et al., submitted]. To more closely examine this correlation, we culled ToxCast data for mitochondrial translocator protein (TSPO; NovaScreen) and mitochondrial membrane potential (MMP) and biomass (Tox21 and Apredica) for a total of 192 chemicals tested for adverse effects on vascular development in transgenic zebrafish embryos [McCollum et al., submitted; Tal et al., submitted]. This set included 40 compounds that disrupted vascular development in zebrafish embryos (zVDC) and 152 compounds that did not. The zVDC set displayed consistent *in vitro* bioactivity on mitochondrial membrane potential (with a Pearson Chi-Square value of 16.92, $p < 0.0001$), but did not have consistent effects on mitochondrial biomass (0.4; $p = 0.527$) or translocator protein ligand binding (0.05; $p = 0.823$). The effect on MMP is consistent with the hypothesis that disruption of the mitochondrial respiratory complexes is a potential mode of action of angiogenic disruptors (complex I for pyridaben, fenpyroxymate, tebufenpyrad, and rotenone; complex III for pyraclostrobin and trifloxystrobin; and complex V for triclocarban). After cytotoxicity correction, the ToxCast bioactivity profiles of 37 of the zVDC could be condensed into 136 gene annotations in a chemical-assay target bipartite network, which revealed clusters associated with Cyp450s, GPCRs, and nuclear receptor signaling, in addition to vascular disruption. These results in the zebrafish model suggest that angiogenic disruptors in the ToxCast library have a positive correlation with mitochondrial respiratory disruption but neither biomass nor TSPO binding. Further analysis is underway to determine if a structural signature or physical property can be identified for these chemical structures [This abstract does not necessarily reflect US EPA policy].