ToxCast and the Next Generation of Risk Assessment: Evaluating how select ToxCast data for the herbicides Propanil and Linuron could be utilized

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Propanil and linuron are widely used herbicides in California (CA). They act by selective inhibition of photosynthetic electron transport in target plants. In mammals, the best characterized toxic modes of action (MOAs) for both herbicides include the oxidation of hemoglobin and the antagonism of androgenic signaling. Pesticide risk assessments depend on endpoints observed in *in vivo* animal studies, human population-based and clinical studies, and mechanistic information. ToxCast data is one major source of mechanistic information from *in vitro* assays based on cellular and molecular steps in known biological pathways. We considered the intrinsic limitations of the *in vitro* ToxCast assays to predict the behavior of complex biological systems. Available *in vitro* ToxCast results were evaluated for their use in support of critical toxicity endpoints from *in vivo* animal studies. *In vivo* toxic effects of linuron and propanil include hematological effects (e.g. methemoglobinemia and hemolytic anemia) as well as incidence of testicular tumors in male rats. While there are no current ToxCast assays that test for methemoglobin-mediated hematologic toxicity of either compound, ToxCast data confirmed the anti-androgenic activities and provided support for a putative common MOA for the induction of testicular tumors *in vivo*. Additionally, ToxCast assay data show that both compounds perturb diverse signal transduction pathways at multiple levels and can directly affect the catalytic activities of proteins involved in detoxification (e.g., both propanil and linuron are androgen receptor antagonists, modulate the activities of multiple transcription factors, and inhibit multiple CYP enzymes). In conclusion, the high-throughput *in vitro* toxicity data from ToxCast may be used to elucidate MOAs and adverse outcome pathways (AOPs) for human risk assessment. Pesticides like propanil and linuron with rich *in vivo* databases could be part of a data pool to test the ability of ToxCast data in predicting *in vivo* adverse effects. Note: The opinions are the authors' and do not necessarily reflect the policies of Cal EPA.